

Atopic dermatitis: The updated practice parameter and beyond

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ABSTRACT

An update to the atopic dermatitis (AD) practice parameter was published in 2013 using an established grading system for determining category of evidence and strength of recommendation. Since the previous update in 2004, a number of seminal observations regarding skin barrier and immune dysregulation in AD have been made with important therapeutic implications. A key addition to the treatment algorithm based on our understanding that normal-appearing skin in patients with AD is not normal is proactive therapy. Studies with both topical steroids and a topical calcineurin inhibitor have shown that in patients with relapsing AD, if they are able to clear or almost clear their eczema, then twice-weekly proactive treatment of normal-appearing skin that tends to flare leads to better disease control. For difficult-to-manage patients, the value of wet wrap therapy is reaffirmed in the practice parameter update. In addition, allergen immunotherapy is now a consideration in select patients with AD and aeroallergen sensitivity. Beyond the practice parameter, novel approaches to filaggrin deficiency are being evaluated. With respect to immune dysregulation, dupilumab, a fully human monoclonal antibody directed at the IL-4 receptor alpha subunit was recently shown to be effective in treating adults with moderate-to-severe AD.

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Atopic dermatitis (AD) is a common, complex chronic inflammatory skin disease.¹ The 2003 National Survey of Children's Health reported prevalence up to 18% in the United States.² In addition, data from over one million children in 97 countries suggests that AD is a global health problem not only in developed countries, but also in developing countries.³ In a review of epidemiology, risk factors associated with increased prevalence included higher socioeconomic status, higher level of family education, smaller family size, and urban environment.⁴ Of note, a recent study found that fewer patients than previously thought outgrow their AD.⁵ In this cross-sectional cohort study of a nationwide long-term registry of children with AD enrolled in the Pediatric Eczema Elective Registry, not until age 20 years did 50% of patients have at least 1 lifetime 6-month symptom- and treatment-free period. Given the importance of this disease, the current update to the AD practice parameter was written by specialists in allergy-immunology, dermatology, and psychology, both from the United States and Europe, using a critical approach with best-evidence-based data (Table 1).⁶

WHY AN UPDATE?

The previous update to the AD practice parameter was published in 2004.⁷ Since then, a number of critical observations have been made, adding to our understanding of AD. These address both immune dysregulation and epidermal barrier abnormalities and have important therapeutic implications.¹ Loss-of-function mutations in the gene (*FLG*) encoding filaggrin, a key epidermal barrier protein, have been shown to be strongly associated with risk for AD in a number of ethnically diverse populations.⁸ Epidemiological data from large birth cohort studies shows that patients with *FLG* mutations have an increased risk for early onset, severe, and persistent AD and also are at increased risk for developing asthma and allergic sensitizations.⁹ Of note, having an *FLG* mutation is associated with a higher odds ratio for allergic sensitization to peanut (5.3) than for AD (3.1).¹⁰ Although *FLG* mutations are the strongest risk factor for AD currently identified and occur in ~ 50% of patients with severe AD, not all patients with AD have *FLG* mutations and even those with mutations may appear to outgrow their disease.⁹ Patients with AD can have decreased filaggrin expression in their skin because of cytokine dysregulation.¹¹ The Th2 cytokines IL-4 and IL-13 have been shown to down-regulate *FLG*, pointing to the intertwined roles of genetically determined barrier and immune abnormalities.¹ These observations suggest that new therapeutic approaches will need to address both skin barrier and immune abnormalities.

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Table 1 Classification of recommendations and evidence

Category of evidence

- Ia. Evidence from meta-analysis of randomized controlled trials
- Ib. Evidence from at least one randomized controlled trial
- IIa. Evidence from at least one controlled study without randomization
- IIb. Evidence from at least one other type of quasi-experimental study
- III. Evidence from nonexperimental descriptive studies, such as comparative studies
- IV. Evidence from expert committee reports, opinions, or clinical experience of respected authorities or both

Strength of recommendation

- A. Directly based on category I evidence
- B. Directly based on category II evidence or extrapolated recommendation from category I evidence
- C. Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D. Directly based on category IV evidence or extrapolated recommendation from category I, II, or III evidence

Source: Ref. 6.

WHAT IS NEW IN FIRST-LINE MANAGEMENT?

Approach to diagnosis and management of patients with AD is outlined in an annotated flow diagram (Fig. 1). Box 5 in the figure lists the approach to conventional therapy. The safety and efficacy of appropriately used topical steroids and topical calcineurin inhibitors (TCIs) in first-line management of AD was confirmed in the practice parameter update with the highest strength of recommendation A.⁶ Nevertheless, it is important for clinicians to recognize that patients, caregivers, and providers continue to express concerns about using these topical medications.^{12,13} Patients and caregivers frequently delay use of these medications after onset of an eczema flare.¹² Thus, it is important to review when a medication was started, where it was applied, and how much was used before deciding that a treatment has failed. Although a boxed warning was added to the package insert for TCIs by the Food and Drug Administration in 2006, there has been no change to the label with respect to indications for use in patients aged ≥ 2 years. Safety of TCIs has been reported in large cohorts ($n = 293, 253$)¹⁴ and a favorable benefit to risk profile has been supported by a number of national and international organizations.¹⁵

A therapeutic option added to box 5 (Fig. 1) in the current update is the addition of dilute bleach baths twice weekly to reduce the severity of AD, especially in patients with recurrent skin infections (A) (Table 1). Note that this recommendation was based on a single published controlled study in children.¹⁶ Patients were treated with dilute bleach baths (one-half cup of bleach in 40 gal of water) twice weekly as well as with intranasal mupirocin (5 days/mo) and had significantly decreased severity of AD at 1 and 3 months compared with placebo as assessed by the Eczema Area and Severity Index (EASI). Patients should be told that this treatment can be drying and irritating to the skin.

Patients and caregivers continue to wonder about food allergens as triggers for AD. Of note, a recent study found that of five common food allergens, only IgE level to egg white correlated significantly with eczema severity in young children with AD.¹⁷ With respect to the role of food allergy in AD, the practice parameter update summary statement 34 states, "The clinician might consider food allergens as triggers of AD more commonly in young infants and children." (D) (Table 1).⁶ The practice parameter references the Food Allergy Expert Panel that suggested consideration of limited food allergy testing in children with persistent AD despite optimized management and topical therapy, in patients with a reliable history of an immediate allergic reaction after ingestion of the food, or both.¹⁸ The practice parameter further states that clinicians should not recommend extensive elimination diets based only on positive allergy skin or *in vitro* tests results (B) (Table 1).⁶ Of note, a retrospective study evaluated the results of food challenges in predominantly AD patients (96%) who were avoiding foods due to suspected allergy based primarily on *in vitro* testing.¹⁹ Of 364 supervised oral food challenges, 325 (89%) were reported as negative. A rational approach to evaluation of suspected food allergy in patients with AD was recently reviewed (Fig. 2).²⁰

MOVING FROM REACTIVE TO PROACTIVE THERAPY

An important change in our approach to treatment of patients with chronic, relapsing AD has been a move from reactive to proactive therapy. Normal-appearing skin in patients with AD is often colonized by *Staphylococcus aureus* and has been shown to have both immune and skin barrier abnormalities.^{21,22} A number of clinical trials have indicated that once control of acute AD is achieved, long-term control can be maintained with twice-weekly application of a topical steroid or TCI applied to areas that appear clear but are prone to eczema flares.²³ Most of the published studies have been performed with either fluticasone cream or tacrolimus ointment. Box 7 (Fig. 1) in the updated prac-

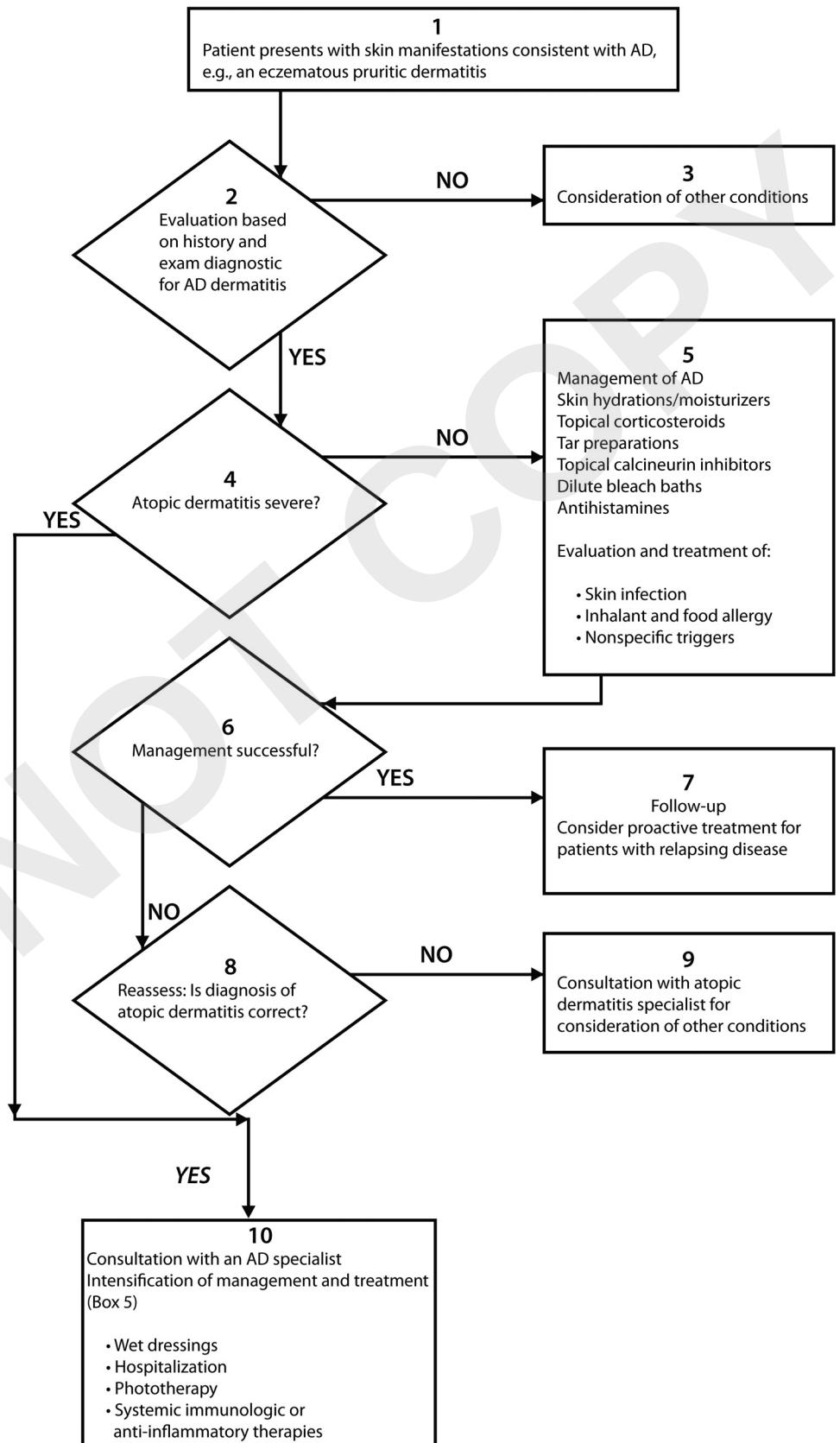
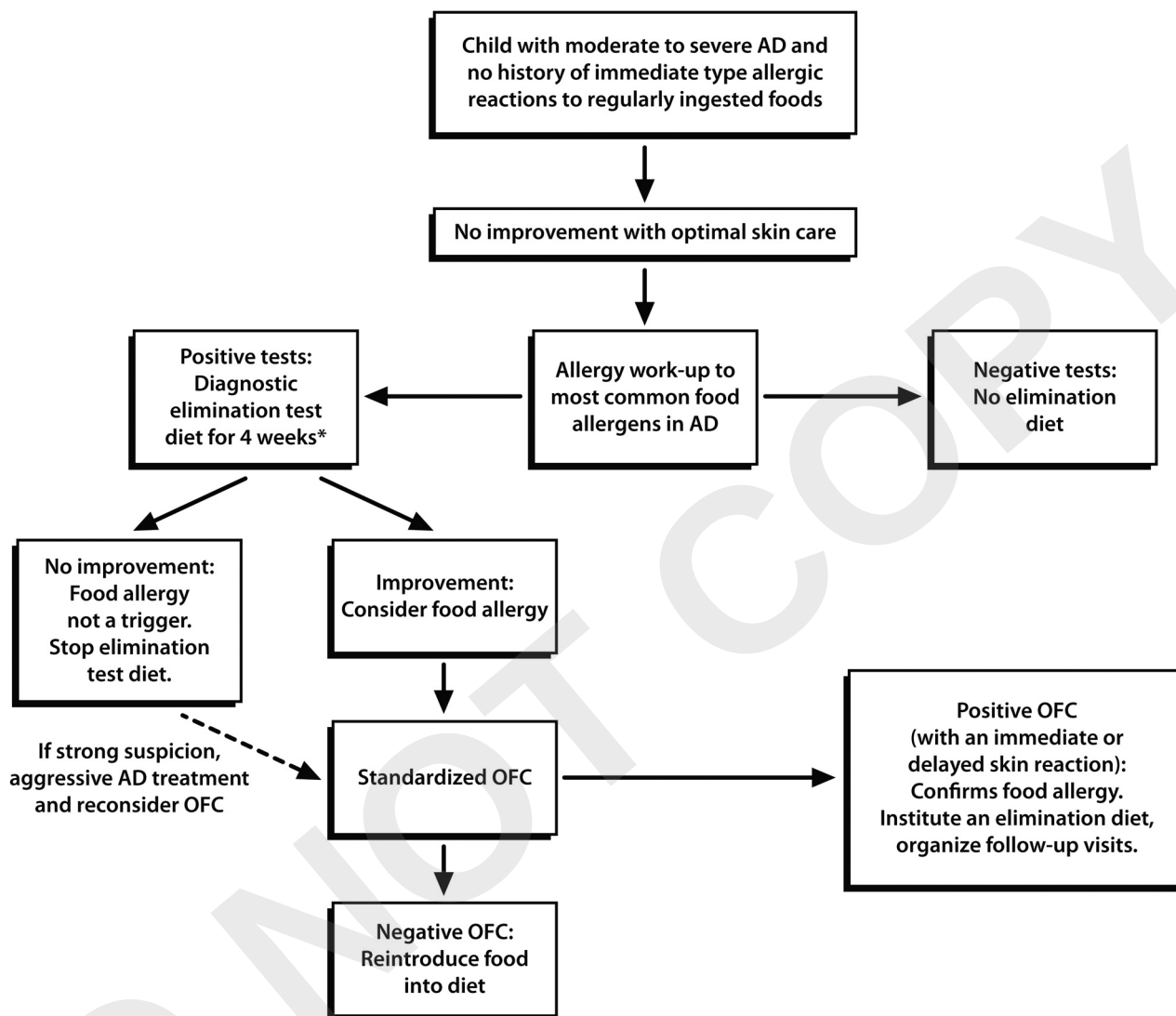


Figure 1. Flowchart of the diagnosis and management of atopic dermatitis (AD; reproduced with permission from Ref 6).



* When practical, to a limited number of foods (see additional comments in text)

Figure 2. Algorithm for the investigation of foods potentially triggering eczema in a child with moderate-to-severe atopic dermatitis (AD; reproduced with permission from Ref. 20).

tice parameter recognizes the value of such an approach.⁶ Although this approach would be considered off-label therapy in the United States, topical tacrolimus is approved for use in Europe as twice-weekly maintenance/proactive therapy in patients as young as 2 years of age for up to 12 months. Of note, this approach was found to be cost-effective for both children and adults with moderate and severe AD from the perspective of the United Kingdom's National Health Service versus a reactive approach.²⁴

MANAGEMENT OF RECALCITRANT PATIENTS

The practice parameter update recognizes the importance of referring patients refractory to first-line therapy to an AD specialist (box 10, Fig. 1).⁶ Although some clinicians would move quickly to prescribing

systemic therapy for such patients, it is important to review a patient's/caregiver's understanding of their prescribed conventional therapy and address potential irritant, allergic or microbial triggers.²⁵ Addressing the psychosocial aspects of a chronic, relapsing illness that can impact sleep and quality of life is also critical to successful management.²⁶

Wet wrap therapy (WWT) may be a useful therapy in combination with topical corticosteroids for treatment of refractory AD (A) (Table 1).⁶ WWT can contribute to skin barrier healing, increase the efficacy of topical steroids, decrease itch sensation, and protect the skin from damage caused by scratching. Overuse can result in skin maceration or skin infection such as folliculitis. WWT for the face requires skilled nursing education of the patient/caregiver. A detailed step-by-step protocol

for WWT as used in the AD program (ADP) at National Jewish Health in Denver, CO, has been described.²⁶ This includes use of a wet layer of cotton/cotton blend clothing (e.g., long underwear and athletic socks) applied over a topical steroid with a dry layer applied on top. A recent study involving the largest population of children with moderate-severe AD treated with WWT and assessed with scoring atopic dermatitis (SCORAD) and a questionnaire as part of a multidisciplinary evaluation in the ADP showed that WWT used on average for 4 days resulted in significant improvement in SCORAD and, importantly, appeared to have a prolonged benefit even after discontinuation based on questionnaire data 1 month after discharge.²⁷ Of note, all 72 patients had failed multiple therapies before admission to the ADP and none required systemic immunosuppressive therapy during the ADP evaluation.

The practice parameter update reviews the benefits and risks of phototherapy as well as a number of systemic immunomodulators, including cyclosporine, mycophenolate mofetil, and methotrexate (A) (Table 1).⁶ Of note, allergen-specific immunotherapy is now presented as a therapeutic option for difficult-to-manage patients with allergic sensitization, rather than as an investigational treatment for AD (B) (Table 1). This is based on several studies of dust-mite immunotherapy and supported by summary statement 8 from the immunotherapy practice parameter.²⁸

BEYOND THE PRACTICE PARAMETER: NEW DIRECTIONS IN TREATING AD

New insights into skin barrier and immune dysregulation should provide novel therapeutic targets. In a recent study, the authors screened a library of >1000 compounds to identify candidate molecules promoting *FLG* mRNA expression.²⁹ JTC801, a nonpeptidergic opioid receptor-like 1 antagonist was shown to promote *FLG* mRNA expression in HaCaT cells (human immortalized keratinocyte cell line), as well as in normal human epidermal keratinocytes. Of interest, JTC801 promoted the expression of *FLG* but not that of other markers for keratinocyte differentiation including loricrin, keratin 10, or transglutaminase 1 in a human skin equivalent model. Oral administration of JTC801 promoted protein levels of filaggrin and suppressed development of AD-like skin inflammation in NC/Nga mice *in vivo*. In a different approach, a single repeat of the murine filaggrin gene was covalently linked to a cell-penetrating peptide and cloned into a bacterial expression system for protein production.³⁰ Immunohistochemical staining of a reconstructed human epidermis tissue model identified penetration of the recombinant filaggrin to the stratum granulosum (the epidermal layer at which filaggrin deficiency is

thought to be pathologically relevant). *In vivo* application to filaggrin-deficient flaky tail (ft/ft) mouse skin showed internalization and processing of recombinant filaggrin to restore the normal phenotype. These results suggest that topically applied filaggrin monomers linked to a cell-penetrating peptide could be internalized by the appropriate cell type and processed to a size similar to wild-type functional peptide to restore epidermal barrier function. Both of these approaches require appropriate evaluation in human trials.

Treatments aimed at addressing the immune dysregulation in AD include dupilumab, a fully human monoclonal antibody directed at the IL-4 receptor α -subunit that blocks both Th2 cytokines IL-4 and IL-13. Dupilumab was previously shown to be effective in a subset of adults with asthma.³¹ More recently, the results of several controlled studies in adults with moderate-severe AD, including two 4-week trials and one 12-week trial with dupilumab monotherapy, showed rapid, dose-dependent clinical improvement.³² In the 12-week trial, 85% of patients in the dupilumab group versus 35% in the placebo group had a 50% reduction in their EASI ($p < 0.001$). In addition, 40% of patients treated with dupilumab compared with 7% in the placebo group had an investigator's global assessment score of 0 to 1 (clear or almost clear; $p < 0.001$). Pruritus scores decreased by 55.7% in the dupilumab group versus 15.1% in the placebo group ($p < 0.001$). In a 4-week combination study of dupilumab or placebo plus topical steroids reported in the same publication, 100% of the patients in the dupilumab group versus 50% in the placebo group had a 50% reduction in their EASI ($p = 0.002$), despite the fact that patients treated with dupilumab plus topical steroids used less than one-half the amount of topical steroids used by those in the placebo plus topical steroid group ($p = 0.16$).

CONCLUSIONS

The current practice parameter update attempts to synthesize the progress in our understanding of the complex skin barrier and immune dysregulation in AD. The update uses a best-evidence-based data approach with summary statements and supporting text ranked by category of evidence and strength of recommendation. An annotated flow diagram has been updated to assist the clinician with diagnosis and management of patients with AD. Addition of a proactive approach for a subset of patients with relapsing disease is the most important addition to this flow diagram. Management of recalcitrant patients includes use of WWT, systemic immunosuppressive treatments, and allergen-specific immunotherapy in appropriate patients. Treatments addressing the filaggrin deficiency in AD are still investigational. A novel therapy that

likely will become incorporated into clinical practice is dupilumab, a monoclonal antibody directed at the IL-4 receptor α -subunit that blocks both Th2 cytokines IL-4 and IL-13.

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