

Management of Severe Atopic Dermatitis in Pediatric Patients



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Learning objectives:

1. To describe the optimal management of severe atopic dermatitis in pediatric patients addressing inflammation, pruritus, sleep disturbance, comorbidities, and quality of life.

2. To apply severity evaluation of atopic dermatitis in clinical practice.

3. To use various treatments options for pediatric patients with severe atopic dermatitis.

4. To recommend appropriate nonpharmacologic interventions for severe pediatric atopic dermatitis.

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EPD, Pola Pharma, Sanofi, Shiseido Japan, Sumitomo Dainippon Pharma, Taiho Pharma, Teijin Pharma, ThermoFisher Scientific, and Torii Pharmaceutical Co., Ltd; and is a consultant for AbbVie, Maruho, Mylan EPD, and Regeneron Pharmaceuticals, Inc/Sanofi Genzyme. L. F. Eichenfield is a consultant and/or investigator for AbbVie, Asana, Amgen, Almirall, Cutanea, Dermavant, Dermira, Forte Biosciences, Galderma, Glenmark/Ichnos, Incyte, Leo Pharma, Lilly, Otsuka, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and Ortho Dermatology. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used

AD- Atopic dermatitis
BEEP- Barrier Enhancement for Eczema Prevention
BSA- Body surface area
EASI- Eczema Area and Severity Index
FDA- Food and Drug Administration
IGA- Investigator Global Assessment
JAK- Janus kinase
MTX- Methotrexate
NB-UVB- Narrow-band ultraviolet B
PDE-4- Phosphodiesterase-4

Atopic dermatitis is a common, chronic inflammatory skin disorder, present in about 12% of children worldwide.

Optimizing management of severe atopic dermatitis in pediatric patients is critical to reduce signs of inflammation, alleviate pruritus and sleep disturbance, minimize the development and/or impact of comorbidities, and improve the patient and caregiver's quality of life. Evaluating the longitudinal severity of pediatric atopic dermatitis is an important component of measuring therapeutic response and long-term management, and is different in clinical practice versus clinical trials. This article describes when and how to use different treatments for pediatric patients with severe atopic dermatitis, including topical medications, phototherapy, and systemic medical therapies (traditional immunosuppressants, biologics, and small molecule inhibitors). It also provides recommendations useful in clinical practice for nonpharmacologic interventions for pediatric patients with severe atopic dermatitis. © 2021 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:1462-71)

Key words: Atopic dermatitis; Therapeutics; Immunosuppressive agents; Phototherapy; Biologics

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic dermatosis that develops most commonly during early infancy and childhood but is seen at all ages. In most cases, it is associated with a personal or family history of atopy, including allergic rhinitis or asthma, and may be associated with multiple comorbidities. Pathogenesis broadly includes abnormalities in skin barrier function and immune dysregulation. Cutaneous features of severe pediatric AD include acute, subacute, and chronic inflammation, characterized by erythematous patches and plaques with scaling, excoriations (from scratching), lichenification (from disease chronicity), and occasional erythroderma (Figure 1). AD therapy is determined by the patient's age, symptoms, comorbidities, and the extent and distribution of the disease. Goals of AD management include educating patients and families, improvement in symptoms and signs of AD, minimizing pruritus, reducing frequency and degree of flares, improving quality of life, and minimizing the development and/or impact of associated comorbidities. The evolution of management of severe AD in children and adolescents is dynamic, with the introduction and active study of multiple new topical and systemic agents, including biologic agents, Janus

kinase (JAK) inhibitors, phosphodiesterase-4 (PDE-4) inhibitors, tapinarof, and microbiome-based interventions.

EPIDEMIOLOGY

AD is a common, chronic inflammatory skin disorder affecting about 10% of children in the United States and about 12% of children worldwide.¹ In 2007, a national survey of children aged 0 to 17 years revealed that about 7% of children with AD were considered severe.² Children with severe AD were more likely to have persistent disease beyond childhood.³

SEVERITY CLASSIFICATION

There is no universally accepted pediatric AD severity measure for use in clinical practice or research. Clinical research studies often capture the SCORing of Atopic Dermatitis index, the Eczema Area and Severity Index (EASI), and/or the more recent Validated Investigator Global Assessment for Atopic Dermatitis, with validation performed in mixed populations of adults, adolescents, and children.^{4,5} The global Harmonising Outcome Measures for Eczema initiative is an international group of experts who have identified the EASI score and other outcomes measures with adequate validity, responsiveness, internal consistency, and intraobserver reliability.⁶ EASI scores can assign subjects in trials to clear, almost clear, mild, moderate, and very severe.⁷ AD may also be considered moderate-severe when there is a minimum of 10% body surface area (BSA) involvement, although involvement of highly visible or functional areas and significantly impaired quality of life are other features that affect severity.⁸ BSA can be estimated using the hand method (the child's extended hand, including palm and fingers, represents 1% of the total BSA) or "Rule of 9's." The Patient-Oriented Eczema Measure and Children's Dermatology Life Quality Index are helpful tools to gauge disease severity and response to treatment from the patient's perspective.

In clinical practice, assessment of AD as severe may include extent of lesions, quality of lesions (eg, erythema, induration, lichenification, and excoriation), frequency of flares, pruritus, sleep disturbance, response to therapy, and difficulty with long-term disease control, psychological conditions (eg, anxiety, depression, and self-esteem), impact on school, work, and leisure activities, and comorbidities. Simpler composite measures have recently been proposed that could be rapidly assessed in clinical practice, including the product of the Investigator Global Assessment (IGA) and the BSA (IGA × BSA), which correlates strongly with the EASI in pediatric AD.⁹ The peak pruritus numerical rating scale is a useful, validated single-item patient-reported outcome of worst itch severity, with a scale of 0 ("no itch") to 10 ("worst itch imaginable"), and can easily be used in clinical practice.¹⁰ The authors find it useful at least noting a global score and/or BSA (objective measures) along with assessing the impact of the disease on quality of life, including itch numerical rating scale and sleep disturbance, or having the patient/parent capture the Patient-Oriented Eczema Measure score when evaluating AD in pediatric patients.

TOPICAL THERAPY

Topical corticosteroids are the first-line treatment for acute flares of AD. Severe disease typically warrants medium- to high-potency topical corticosteroids twice daily for a few days beyond clearance. Lower potency steroids or nonsteroidal topical

medications may be prescribed for sensitive areas or younger children. Soak and seal or wet wrap therapy are useful for more severe disease. Wet wrap therapy involves the application of topical therapy on the affected skin, covered by a wet layer of bandage, gauze, or a cotton garment, and then wrapped by an outer dry layer.¹¹ If there is lack of improvement, one may need to consider nonadherence, infection, or contact allergy to medications.¹² In rare cases, hospitalization is indicated for an intense regimen of wet wrap therapy and treatment of any superinfection.

Parental education is critical for appropriate management of AD. Steroid phobia often leads to poor compliance with recommended therapies. A short 2-day educational program had a significant impact on the disease severity and parental concerns over corticosteroids, but interestingly, it did not influence the amount of corticosteroid used.¹³

Once the flare is under control, proactive intermittent topical corticosteroids are helpful to prevent exacerbations. For maintenance, topical corticosteroids can be used 1 to 3 times per week.¹² However, if frequent steroid use is anticipated, topical nonsteroidal anti-inflammatory agents with a lower risk of long-term side effects should be considered. These include topical calcineurin inhibitors (tacrolimus and pimecrolimus) and the PDE-4 inhibitor crisaborole. Topical tacrolimus and pimecrolimus are Food and Drug Administration (FDA)-approved for use in children 2 years and older with moderate to severe and mild to moderate AD, respectively. Although both tacrolimus and pimecrolimus have had a black box warning for a theoretically increased risk of lymphoma, studies during the past 20 years have not shown evidence of an increased risk of malignancy.^{14,15} Crisaborole was FDA-approved in March 2020 for children 3 months and older for the treatment of mild to moderate AD. The phase IV open-label study demonstrated that the use of crisaborole in young children resulted in close to a 60% reduction from baseline in EASI scores.¹⁶ Both topical calcineurin inhibitors and crisaborole have a common side effect of burning and stinging with initial application, particularly when used on sensitive skin areas such as the eyelids, a frequently affected site for AD, which limits their use. Other PDE-4 topical agents in clinical studies for pediatric AD include difamilast and roflumilast.

Currently in development are topical JAK inhibitors ruxolitinib and delgocitinib. Ruxolitinib, which predominantly suppresses JAK-1 and JAK-2 signaling, has shown promising results in 2 phase III clinical trials for patients 12 years and older with mild to moderate AD.¹⁷ Delgocitinib ointment, a pan-JAK inhibitor approved in Japan for AD in patients 16 years and older, has demonstrated more than 50% improvement in modified EASI scores after 4 weeks in Japanese children aged 2 to 15 years in a phase II trial.¹⁸ Tapinarof, a therapeutic aryl hydrocarbon receptor modulating agent, has shown evidence of efficacy and safety in a phase II clinical trial of adults and adolescents with moderate to severe AD.¹⁹ Topical JAK inhibitors and tapinarof appeared highly tolerable, with low rates of burning/stinging in the clinical trials.

The cutaneous microbiome is intimately associated with the epidermal function. In patients with AD, *Staphylococcus aureus* predominates during disease flares with a decrease in microbiome diversity and greater AD severity is associated with less microbiome diversity.²⁰ Coagulase-negative staphylococci with anti-*S aureus* activity are common on the skin of healthy human

subjects, but much less frequent on those with AD. Interventions with reintroduction of commensal strains can decrease *S aureus* colonization in subjects with AD.²¹ Several early clinical trials suggest that targeting the microbiome through topical application of commensal organisms, including *Staphylococcus hominis* and *Roseomonas mucosa*, reduce *S aureus* colonization, skin inflammation, and AD severity.^{22,23} Two open-label studies involving 5 adults and 20 children with AD assessed the topical treatment of *R mucosa*. Results showed significant decreases in measures of disease severity, topical steroid requirement, and *S aureus* burden, with no adverse events.^{24,25} Double-blind, placebo-controlled studies are needed and topical commensals are not currently available.

PHOTOTHERAPY

Phototherapy with narrow-band ultraviolet B (NB-UVB) is an appropriate second-line therapy for patients with moderate to severe AD that is refractory to intensive topical regimens. It is most feasible for older children, typically aged at least 5 to 6 years, who can cooperate with treatment. The favorable safety profile compared with systemic agents is often appreciated by parents, with adverse event rate thought to be similar to that in adults and overall quite mild.²⁶ Inconvenience of 2 to 3 times weekly in-office treatments is a barrier for many school-age children and working parents. Home-phototherapy devices may be an option for patients with insurance coverage, typically after they have successfully used in-office phototherapy. NB-UVB has a slow onset of efficacy and is best considered as a maintenance therapy that is not useful for acute flares. Although ultraviolet A1 and psoralen plus ultraviolet A have also been shown to be effective, NB-UVB is typically preferred because of its more favorable safety profile and accessibility.²⁷

In 1 study of 50 children who completed more than 10 NB-UVB treatments administered 3 times weekly for their AD, 40% of patients achieved complete clearance or minimal residual disease, good improvement was achieved in 23%, and moderate improvement in 16%, determined by the same dermatologist.²⁸ Another study of 30 children (age 4-14 years) with moderate to severe AD demonstrated a significant reduction in SCORing of Atopic Dermatitis index compared with baseline as well as significant improvement in pruritus and sleep loss.²⁹

SYSTEMIC THERAPIES

The decision to start a systemic therapy for a patient with AD is difficult, and many factors must be taken into consideration. A subgroup of the International Eczema Council with experts from 9 countries created a consensus statement as a recommended approach to this decision, which although not specifically discussing pediatric patients has been used effectively for pediatric patients.³⁰ The International Eczema Council statement recommends consideration of the following for patients with severe AD (based on cutaneous extent as well as impact on quality of life) before initiation of a systemic medication:

1. Has adequate patient education been provided?
2. Has the diagnostic workup been completed, including the following: have alternative diagnoses been considered, have infections been treated, has patch testing been considered, and is referral to Allergy warranted?
3. Has intensive topical therapy been given an adequate trial, including wet wrap or soak and seal techniques?



FIGURE 1. Severe AD.

4. Has phototherapy been considered or given a trial?

This algorithm can be helpful in determining the appropriate patients in whom to start systemic therapy, with the choice of therapy based on age, lifestyle, comorbidities, and patient/family preference.³⁰

A 2016 survey of prescribing practices of Society of Pediatric Dermatology members in the United States and Canada was completed by TREATment of severe Atopic dermatitis in children Taskforce.³¹ Among those who completed the survey, cyclosporine (45.2%), methotrexate (MTX) (29.6%), and mycophenolate mofetil (13%) were the first-line drugs of choice.³¹ A similar survey performed by the European TREATment of severe Atopic dermatitis in children Taskforce in 2013 showed first-line drugs of choice including cyclosporine (43.0%), corticosteroids (30.7%), and azathioprine (21.7%).³² A database assessment of treatment by any health care provider (including dermatologist, allergist/immunologist, primary care providers, etc) of 607,258 pediatric AD patients from 2011 to 2016 shows that systemic immunosuppressants were rarely prescribed (<0.5%), whereas systemic corticosteroids were prescribed in 24.4% of patients.³³ Of these therapies, only systemic corticosteroids are approved for use in pediatric AD. However, it is highly evident that the rank ordering of utilization of systemic agents has changed greatly since approval of dupilumab for pediatric patients in the United States. Table 1 outlines available systemic therapies that are used for moderate to severe AD.

Systemic corticosteroids

Before the FDA approval of dupilumab, systemic corticosteroids were the only FDA-approved systemic therapy for AD. Systemic corticosteroids are frequently used given their quick onset and impressive efficacy even in severe disease. However, specialists commonly avoid using systemic corticosteroids due to the multiple and generally severe adverse effects, as well as the rebound flares that are seen after cessation. The International Eczema Council published a consensus statement of the 77 participating members in 2018, stating that systemic

corticosteroids should generally be avoided, but short-term use of systemic corticosteroids can be used in rare circumstances for severe AD, including lack of other treatment options, as a bridge to systemic therapy or phototherapy, during acute flares in need of immediate relief, or in anticipation of a major life event.³⁴ Most on the council (57%) agreed that systemic corticosteroids should be avoided for AD in pediatric patients younger than 12 years.³⁴

Cyclosporine

Cyclosporine is a calcineurin inhibitor that blocks transcription of cytokines and decreases activation of T lymphocytes. It is an efficacious treatment option with a rapid onset of action compared with other steroid-sparing agents, with response often seen within 2 to 3 weeks. However, continuous therapy beyond 1 year is typically not recommended and it is unknown how many short courses can be given. Cyclosporine should be gradually tapered to prevent flaring, often while starting another agent. Cyclosporine is typically dosed at 2.5 to 5 mg/kg/d; some experts prefer cyclosporine microemulsion at 3 mg/kg/d.

Cyclosporine is generally well tolerated in the pediatric population, with an overall lower number of associated comorbidities compared with adults. The 2 most notable side effects include nephrotoxicity and hypertension, which are dose and duration dependent, and may require dose adjustment. Other adverse effects include possible increased risk of malignancy, including nonmelanoma skin cancer, gastrointestinal upset, hyperlipidemia, hyperuricemia, hypomagnesemia, and hyperkalemia. Thus, careful blood pressure and lab monitoring is essential, with frequencies varying widely among experts. A systematic review of oral cyclosporine in patients with severe AD included 5 studies and 602 patients, showing similar efficacy in adults and children, although tolerability may have been better in children.³⁵

Methotrexate

Low-dose MTX is an alternate immunosuppressive therapeutic option for severe AD that does not respond to topical therapies. MTX is a folic acid antagonist that inhibits dihydrofolate reductase, thereby inhibiting cell division and lymphocyte proliferation, resulting in anti-inflammatory effects. Compared with cyclosporine and systemic corticosteroids, it has a slower onset of action, with results typically seen after a minimum of 6 weeks of treatment. Dosing in children with AD typically ranges from once weekly 0.2 to 0.7 mg/kg administered orally (more commonly used due to ease of administration) or subcutaneously (less gastrointestinal side effects; however, weekly injections can be difficult in children), with a maximum dose of 25 mg weekly. The injectable solution can be given orally in younger children who cannot swallow the pills; there is also a newly approved oral MTX solution on the market. It is administered with folic acid 1 mg daily except the day of MTX administration to reduce MTX toxicity, including decrease in nausea, vomiting, diarrhea, liver function test abnormalities, and risk of pancytopenia. Laboratory monitoring is required given these potential side effects, but the frequency of testing varies among dermatologists. Although MTX is generally well tolerated, common side effects include gastrointestinal upset, headache, fatigue, and dizziness for 1 to 2 days after the weekly dose. Rare but serious adverse effects include hepatotoxicity, life-threatening pancytopenia during the first 4 to 6 weeks of

TABLE I. Systemic therapies for moderate to severe AD

Medication	General indication for use	Dosing and frequency	Monitoring	Onset of efficacy	Common adverse effects	Serious adverse effects
Systemic corticosteroids	Should generally avoid, exceptions include as a bridge to other therapy, concomitant allergic contact dermatitis, major life events, etc	0.5-1 mg/kg/d prednisone tapered over 2-4 wk	Not needed for short courses	Rapid, within days to weeks	Increased appetite/weight gain, hyperglycemia, hypertension	Many, including growth impairment, opportunistic infections, osteoporosis
Cyclosporine	First- or second-line therapy for severe AD, including acute flares	2.5-5 mg/kg/d PO divided BID, usually limited to 1 y	CBC, CMP, lipid panel, Mg, uric acid and blood pressure; frequency varies	Rapid, within weeks	Nephrotoxicity and hypertension (dose/duration dependent), increased risk of infection	Possible increased risk of malignancy, GI upset, lab abnormalities
MTX	First- or second-line therapy for moderate to severe AD	0.2-0.7 mg/kg PO weekly, with maximum dose of 25 mg weekly. Folic acid 1 mg on non-MTX days	CBC, CMP-frequency varies	Slow, usually after 6 wk of treatment	GI upset, headache, fatigue, and dizziness 1-2 d after dose	Hepatotoxicity, pancytopenia, idiosyncratic acute pneumonitis, pulmonary fibrosis
Azathioprine	Second- or third-line therapy for moderate to severe AD	1-2.5 mg/kg/d PO, dependent on TPMT activity	TPMT at baseline; CBC, CMP- frequency varies	Slow, weeks to months	GI upset, increased risk of infection	Rare hypersensitivity syndrome, increased risk of malignancy
Mycophenolate mofetil	Second- or third-line therapy for moderate to severe AD	30-50 mg/kg/d divided BID	CBC, CMP-frequency varies	Slow, maximal effect after 8-12 wk	GI upset, increased risk of infection	Myelosuppression, risk of carcinogenesis in transplant patients
Dupilumab	Recently used as first-line therapy for moderate to severe AD in children 6 y and older	Subcutaneous injection: * >60 kg: 600 mg LD followed by 300 mg q 2 wk 30-59 kg: 400 mg LD followed by 200 mg q 2 wk 15-29 kg: 600 mg LD followed by 300 mg q 4 wk	None required	Relatively rapid, early results within weeks and maximal results in 3-4 mo	Injection-site reactions, noninfectious conjunctivitis, exacerbation or new onset of facial redness	Rare reports of anaphylaxis, serum sickness, keratitis, parasitic infections, vasculitis
JAK inhibitors (upadacitinib, abrocitinib, baricitinib)	Not FDA-approved for AD. Clinical trials performed for adolescents and adults with moderate to severe AD	Abrocitinib: 100 or 200 mg PO q day Upadacitinib: 30 mg PO q day in adults Baricitinib: 2-4 mg PO q day	Baseline viral hepatitis screen. CBC, CMP, and lipid panel baseline and periodically	Relatively rapid, some improvement within weeks, full results in few months	Acne/folliculitis, hyperlipidemia, nausea, headaches, nasopharyngitis	Thrombocytopenia, hyperlipidemia, increase in creatine phosphokinase

BID, Twice daily; *CBCd*, complete blood cell count with differential; *CMP*, comprehensive metabolic panel; *GI*, gastrointestinal; *LD*, loading dose; *Mg*, magnesium; *PO*, *per os* (by mouth); *q*, every (ie, day, week); *TPMT*, thiopurine methyltransferase.

*Approved dosing in the United States. May vary in other countries.

therapy, and very rarely, idiosyncratic acute pneumonitis and pulmonary fibrosis.

Pediatric AD studies of MTX are limited and overall of low quality, with only 1 small randomized unblinded controlled trial comparing MTX to cyclosporine, showing overall similar results between the two.³⁶ However, MTX has a slower onset of action compared with cyclosporine; thus, many physicians will start both simultaneously, using a short course of cyclosporine to get faster control of severe disease while overlapping with MTX, which is continued as maintenance therapy. There are several retrospective studies demonstrating MTX as a cost-effective, safe, and efficacious therapy for longer-term control of AD.^{37,38}

Azathioprine

Azathioprine is an immunosuppressive, steroid-sparing agent that inhibits purine synthesis as a 6-mercaptopurine analog. Laboratory monitoring is required because bone marrow suppression and liver toxicity are serious concerns. Additional side effects include gastrointestinal upset, rare hypersensitivity syndrome, infection, and increased risk of infection and malignancy (including lymphoma and squamous cell carcinoma, although it is unclear whether this is relevant at dermatologic doses). Baseline thiopurine methyltransferase allele activity levels must be checked, and azathioprine should be dosed on the basis of result. Dosing in children and adults is generally 2.5 mg/kg/d in patients with normal thiopurine methyltransferase activity, with lower doses (such as 1 mg/kg/d) used for carriers of mutant alleles and/or definite intermediate thiopurine methyltransferase levels. Similar to MTX, it has a relatively slow onset of action compared with systemic corticosteroids and cyclosporine. Evidence of azathioprine for children with AD is limited to a few observational studies.^{39,40}

Mycophenolate mofetil

Mycophenolate mofetil inhibits purine synthesis by binding inosine monophosphate dehydrogenase, thereby inhibiting lymphocyte activation. Common adverse effects include gastrointestinal upset; less common risks include infections, myelosuppression, and a risk of carcinogenesis in transplant patients, but this risk in dermatology patients is unclear.

Two retrospective case series demonstrate efficacy and overall safety of mycophenolate mofetil use for pediatric AD, although numbers are quite low.^{41,42} Heller et al⁴¹ used doses of 40 to 50 mg/kg/d in younger children (likely due to increased surface area-to-volume ratios) and 30 to 40 mg/kg/d in adolescents, with maximal effect after 8 to 12 weeks of therapy. Similar to MTX and azathioprine, mycophenolate mofetil has a slower onset of action and thus is best for maintenance therapy rather than treating an acute AD flare. A recent systematic review and meta-analysis of mycophenolate mofetil demonstrated no difference in treatment outcome rates between adult and pediatric cases.⁴³

Biologics and small molecules

Dupilumab is the first FDA-approved biologic therapy for the treatment of AD, and recently became approved for children aged 6 to 11 years with moderate to severe AD not adequately controlled with topical therapies. It is a monoclonal antibody (mAb) that binds the IL-4 receptor alpha subunit, thus blocking signaling of both IL-4 and IL-13. Dupilumab may be beneficial in patients with several AD-related comorbidities, because it is also approved for moderate to severe asthma in patients 12 years and older with an eosinophilic phenotype or with oral

corticosteroid-dependent asthma, chronic rhinosinusitis with nasal polyps in adults, and is in clinical trials for eosinophilic esophagitis. It is safe for long-term use with a favorable safety profile, superior to that of conventional immunosuppressive agents, and does not require routine lab monitoring. Many pediatric dermatologists now use dupilumab as first-line treatment for moderate to severe AD when topical therapies are not adequate and phototherapy is not sufficient or tenable.

Adverse effects include injection-site reactions, noninfectious conjunctivitis, and exacerbation or new onset of facial redness. Most studies have shown higher rates of conjunctivitis in patients treated with dupilumab than placebo groups; prophylactic treatment with topical eye lubricants has been suggested but not tested for efficacy. For conjunctivitis recalcitrant to conservative measures, treatment can be coordinated with Ophthalmology using ophthalmic topical corticosteroids, tacrolimus, cyclosporine, or lifitegrast.⁴⁴ Facial redness associated with dupilumab was not described in the AD clinical trials, but has been frequently described postmarketing. Several theories have been proposed to explain this phenomenon, including a hypersensitivity reaction to dupilumab, site-specific treatment failure, a seborrheic dermatitis-like reaction to facial *Malassezia* species, or a paradoxical flaring of allergic contact dermatitis. It typically does not require treatment cessation.⁴⁵

Dupilumab is administered as a subcutaneous injection, and the approved pediatric AD dosing is weight-tiered: children 60 kg and over are dosed as adults, with a 600-mg loading dose followed by 300 mg every 2 weeks. Per FDA-approved guidelines, children aged 6 to 11 years and adolescents weighing 30 to 59 kg are dosed with a 400-mg loading dose followed by 200 mg every 2 weeks and children weighing 15 to 29 kg receive a 600-mg loading dose followed by 300 mg every 4 weeks. The European Medicines Agency has approved the 600-mg loading and 300 mg every 4 weeks for children aged 6 to 11 years weighing 15 to less than 60 kg, with flexibility to increase the dosing to 200 mg every 2 weeks.

A phase III randomized trial of 251 adolescents aged 12 to 18 years with severe AD treated with dupilumab showed that a higher proportion of patients receiving dupilumab than placebo achieved 75% or more improvement from baseline in the EASI and an IGA of clear or almost clear.⁴⁶ A recent phase III randomized 16-week trial of dupilumab plus topical corticosteroids showed similar efficacy and side effect profile in children aged 6 to 11 years as in adults with severe AD.⁴⁷ Another phase IIa, open-label study with a phase III open-label extension in adolescents demonstrated long-term safety and efficacy of dupilumab in adolescents for up to 52 weeks of treatment.⁴⁸

Multiple novel therapeutic agents are undergoing clinical trials and development for the treatment of AD. Oral and topical small molecule JAK inhibitors, including upadacitinib, abrocitinib, and baricitinib, show promising early results for pediatric and adult AD, but have not yet received approval for the AD indication. A recent randomized, phase III monotherapy clinical trial was performed with 391 patients 12 years and older (including 40 patients aged 12-18 years) with moderate to severe AD treated with abrocitinib (200 mg or 100 mg), an oral, once-daily JAK 1 selective inhibitor, compared with placebo.⁴⁹ Significantly greater proportions of those treated with abrocitinib than placebo achieved an IGA response of clear or almost clear with improvement of at least 2 grades and/or at least 75% improvement in EASI scores. Adverse events were reported in 65.8% of

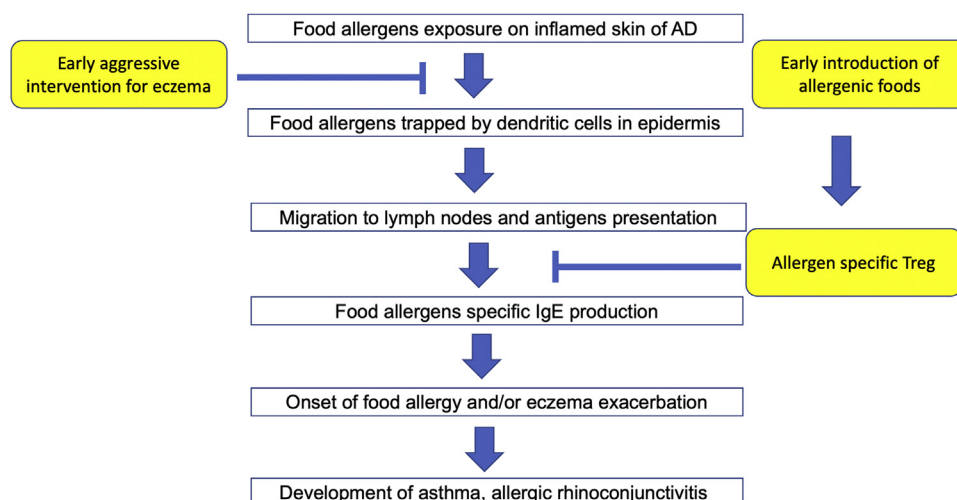


FIGURE 2. Schematic of possible influence of sensitization to food allergens in the development of food allergy and other atopic conditions, and interventions that may modulate this.

patients in the 200-mg group, 62.7% of patients in the 100-mg group, and 53.8% of patients in the placebo group. Nausea was the most commonly reported adverse event in the 200-mg group in 14.2% of patients, whereas nasopharyngitis was the most commonly reported adverse event in the 100-mg group in 12.7% of patients. Mild to moderate acne/folliculitis is the most common adverse event with oral (and topical) JAKs. Notably, thrombocytopenia was reported only in the 200-mg group in 3.2% of patients. Hyperlipidemia and increases in creatine phosphokinase have also been described more often with JAK inhibitors. Upadacitinib as monotherapy has shown efficacy in adults and adolescents with moderate to severe AD, with greatest clinical benefit at the higher 30-mg once-daily dose in a phase IIb randomized trial.⁵⁰ Baricitinib, an oral selective JAK 1 and 2 inhibitor, has shown efficacy in adult patients with moderate to severe AD within 16 weeks of treatment.⁵¹ Use of these JAK inhibitors as a class will almost certainly be limited by black box warnings (serious malignancies, infections, and thrombosis); baricitinib and upadacitinib indications for rheumatoid arthritis have these warnings. Nemolizumab (anti-IL-31 receptor A antibody—studied in individuals 13 years and older with AD and pruritus), lebrikizumab (anti-IL-13 antibody), and tralokinumab (anti-IL-13) are in trials or have recently completed trials in adolescents for the treatment of AD.⁵²

NONPHARMACOLOGIC INTERVENTIONS AND ALLERGIC DISEASE CONSIDERATIONS

Numerous nonpharmacologic interventions have been described to help prevent or mediate the severity of pediatric AD. Liberal use of bland emollients is recommended to all patients with AD to help repair the skin barrier and may prevent disease flares.

Optimal bathing practices for children with AD are yet to be determined. Bathing with water can hydrate the skin but may also lead to transepidermal water loss if left to evaporate without moisturizers.⁵³ In a cohort study of 1303 healthy 3-month-old infants assessing the development of AD, frequent bathing was associated with skin barrier dysfunction and a higher prevalence of AD.⁵⁴ In this study, there was an increase in mean

transepidermal water loss across bathing categories, from up to once weekly to at least daily. However, the data differ for individuals with established, diagnosed moderate to severe pediatric AD. One study by Cardona et al⁵⁵ showed that frequent bathing with immediate application of moisturizers was found to be superior as an acute intervention for moderate to severe pediatric AD, with the SCORing of Atopic Dermatitis decreased by 21.2 compared with the group that bathed less frequently. Bleach baths are frequently recommended by specialists to improve clinical symptoms of AD due to anti-inflammatory and anti-pruritogenic effects.⁵⁶

There is debate whether early intervention affects the development and course of AD. A significant number of children with AD later develop asthma, allergic rhinitis, and/or food allergies, known as the atopic march. It is thought that the march typically starts with AD because the skin barrier defect and/or alterations in the microbiome result in sensitization, which ultimately progresses to the other atopic disorders. However, there may be genetic and/or early environmental risk factors that predispose to the development of atopic diseases in a “cluster” pathway and the march reflects tissue-driven manifestations rather than true progression.⁵⁷ A randomized clinical trial in Norway and Sweden revealed that early skin emollients and/or early complementary feeding of peanut, cow’s milk, wheat, and egg did not reduce the development of AD by age 12 months.⁵⁸ A separate large, 2-year multicenter randomized controlled trial (Barrier Enhancement for Eczema Prevention [BEEP]) assigned 1394 newborns with a family history of AD to the emollient group, provided with emollient for daily application until 1 year of life, or the control group given standard skin-care advice. This study found no evidence that daily emollient during the first year of life prevents AD in high-risk individuals, and may increase the risk of skin infections.⁵⁹ The BEEP trial published in 2020 refuted a smaller trial from 2014 that showed daily emollient therapy to be a safe and effective approach for AD prevention. In this study of 124 neonates at high risk for AD, daily emollient therapy from birth to 6 months of life demonstrated a statistically significant protective effect on the cumulative incidence of AD, with a relative risk reduction of 50% (95% CI, 0.28-0.9; $P = .017$).⁶⁰ An important difference between the BEEP main published in 2020

and the smaller 2014 pilot is adherence. Adherence in BEEP main was defined as satisfactory in the intervention group if emollients were applied at least 3 to 4 times per week to most of the child's body (defined as at least 2 of face and neck, arms and legs, or trunk), and was achieved in 74% of responders at 12 months. Strict adherence defined as 7 days a week of emollient application was achieved in 81% of patients in the intervention group in the pilot study at 24 weeks. Nonadherence was 11% in the BEEP main and 0% in the pilot.^{55,56} Studies are being developed to evaluate whether early aggressive treatment for AD may prevent the development of other atopic diseases by reducing allergen sensitization.⁶¹

There is some evidence suggesting that exclusive breastfeeding for 3 to 4 months decreases the incidence of AD in the first 2 years of life, but insufficient evidence that hypoallergenic hydrolyzed formulas prevent the development of atopic disease.⁶² Maternal diet, dietary supplements, and prebiotics and probiotics do not appear to have a significant impact on pediatric AD.⁶³

Environmental factors, such as irritants, pollutants, and harsh climate, may exacerbate AD flares.⁶⁴ Although children with AD are often IgE sensitized to house dust mites, there is not enough evidence based on the lack of robust clinical trials to recommend reduction and avoidance of house dust mites.⁶⁵

About one-third of patients with moderate to severe AD have IgE-mediated food allergy.⁶⁶ The National Institutes of Health recommends food allergy evaluation for milk, egg, peanut, wheat, and soy for children younger than 5 years with moderate to severe AD with persistent disease despite optimized management and topical therapy and/or history of immediate reaction after ingestion of a specific food.⁶⁷ The Learning Early About Peanut Allergy (LEAP) trial demonstrated that early introduction of peanuts can decrease the frequency of peanut allergy development in infants with atopy.⁶⁸ Updated guidelines indicate that screening for peanut sensitivity is not required before introducing peanuts to an infant's diet.⁶⁹

Importantly, there are reports of strict dietary limitations imposed by parents for their children with AD in attempts to treat their skin disease, which have resulted in nutritional deficiencies, with lower intake of calories, protein, fat, riboflavin, vitamin B₁₂, calcium, phosphorous, and iron, and lower documented serum iron, protein, and albumin values. This has resulted in lower Z scores for weight, height, head circumference, and body mass index.⁷⁰ Children with severe AD may develop hypoproteinemia, probably due to protein loss through damaged skin.⁷¹ This can lead to serious complications such as hypovolemia and failure to thrive.

We should keep in mind that food allergens detected as positive in serum IgE and/or skin prick test are usually not the causes of AD, but indicate the results of sensitization via inflamed skin of AD.⁷²⁻⁷⁴ A retrospective study of 125 pediatric patients, many of whom had active AD, highlighted that 89% of oral food challenges performed on foods avoided because of previous immunoassays were negative and did not exacerbate AD flares, thus distinguishing IgE sensitization from true food allergies.⁷⁵ Severe AD and early-onset AD are strong risk factors of food allergy and allergic comorbidities.⁷⁶⁻⁸⁰ Early introduction of allergenic foods and early aggressive intervention for severe AD may be considered to reduce the likelihood of developing food allergies^{68,80,81} (Figure 2).

CONCLUSIONS

Optimal management of severe AD is critically important given the severe impact on quality of life this condition can have for pediatric patients and their caregivers. Topical therapy with corticosteroids and nonsteroid medications and liberal emollient use are standard of care for initial treatment of all patients with AD. However, many patients with moderate to severe AD require further treatment with phototherapy or a systemic immunosuppressive or immunomodulatory agent. Determining the ideal therapy for a patient is individualized for every patient on the basis of their medical history, severity of disease, symptoms, and an in-depth discussion with the family. There is currently extensive research and development for novel AD therapeutics, and it is likely that management practices will be continuously changing and progressing for the ultimate benefit of our patients.

REFERENCES

1. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. Epidemiology of atopic dermatitis (AD) in children aged 6–11 years: a cross-sectional study in the United States (US), Canada, Europe, and Japan: Revolutionizing Atopic Dermatitis-Virtual Abstract 2020. Available from: https://revolutionizingad.com/images/resources/2020Virtual/Abstracts/177_Silverberg_JI_et_al_Epidemiology_in_Children_Cross_Sequential_Study.pdf. Accessed December 2, 2020.
2. Silverberg JI, Simpson EL. Associations of childhood eczema severity: a US population-based study. *Dermatitis* 2014;25:107-14.
3. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD): a systematic review and meta-analysis. *J Am Acad Dermatol* 2016;75:681-687.e11.
4. Schmitt J, Langan S, Williams HC, Network ED-E. What are the best outcome measurements for atopic eczema? A systematic review. *J Allergy Clin Immunol* 2007;120:1389-98.
5. Simpson E, Bissonnette R, Eichenfield LF, Guttman-Yassky E, King B, Silverberg JI, et al. The Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD): the development and reliability testing of a novel clinical outcome measurement instrument for the severity of atopic dermatitis. *J Am Acad Dermatol* 2020;83:839-46.
6. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol* 2014;134:800-7.
7. Leshem YA, Hajar T, Hanifin JM, Simpson EL. What the Eczema Area and Severity Index score tells us about the severity of atopic dermatitis: an interpretability study. *Br J Dermatol* 2015;172:1353-7.
8. Boguniewicz M, Alexis AF, Beck LA, Block J, Eichenfield LF, Fonacier L, et al. Expert perspectives on management of moderate-to-severe atopic dermatitis: a multidisciplinary consensus addressing current and emerging therapies. *J Allergy Clin Immunol Pract* 2017;5:1519-31.
9. Suh TP, Ramachandran D, Patel V, Jackson KL, Rangel SM, Fishbein AB, et al. Product of Investigator Global Assessment and Body Surface Area (IGxBSA): a practice-friendly alternative to the Eczema Area and Severity Index to assess atopic dermatitis severity in children. *J Am Acad Dermatol* 2020;82:1187-94.
10. Yosipovitch G, Reaney M, Mastey V, Eckert L, Abbé A, Nelson L, et al. Peak Pruritus Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol* 2019;181:761-9.
11. Brar KK, Nicol NH, Boguniewicz M. Strategies for successful management of severe atopic dermatitis. *J Allergy Clin Immunol Pract* 2019;7:1-16.
12. Boguniewicz M, Fonacier L, Guttman-Yassky E, Ong PY, Silverberg J, Farrar JR. Atopic dermatitis yardstick: practical recommendations for an evolving therapeutic landscape. *Ann Allergy Asthma Immunol* 2018;120:10-22.e2.
13. Futamura M, Masuko I, Hayashi K, Ohya Y, Ito K. Effects of a short-term parental education program on childhood atopic dermatitis: a randomized controlled trial. *Pediatr Dermatol* 2013;30:438-43.
14. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. *BMC Pediatr* 2016;16:75.

15. Paller AS, Fölster-Holst R, Chen SC, Diepgen TL, Elmets C, Margolis DJ, et al. No evidence of increased cancer incidence in children using topical tacrolimus for atopic dermatitis. *J Am Acad Dermatol* 2020;83:375-81.
16. Schlessinger J, Shepard JS, Gower R, Su JC, Lynde C, Cha A, et al. Safety, effectiveness, and pharmacokinetics of crisaborole in infants aged 3 to < 24 months with mild-to-moderate atopic dermatitis: a phase IV open-label study (CrisADe CARE 1). *Am J Clin Dermatol* 2020;21:275-84.
17. Papp K, Szepletowski JC, Kircik L, Toth D, Kuligowski ME, Venturanza ME, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from two phase 3, randomized, double-blind studies. *J Skin* 2020;4:s95.
18. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Oda M, Kabashima K, et al. Phase 2 clinical study of delgocitinib ointment in pediatric patients with atopic dermatitis. *J Allergy Clin Immunol* 2019;144:1575-83.
19. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, et al. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol* 2019;80:89-98.e3.
20. Paller AS, Kong HH, Seed P, Naik S, Scharschmidt TC, Gallo RL, et al. The microbiome in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019;143:26-35.
21. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med* 2017;9:eaah4680.
22. National Institutes of Health Clinical Center, National Institute of Allergy and Infectious Diseases. Beginning assessment of cutaneous treatment efficacy of Roseomonas in atopic dermatitis. 2017. Available from: <https://clinicaltrials.gov/ct2/show/NCT03018275?id=NCT03018275>. Accessed December 4, 2020.
23. National Institute of Allergy and Infectious Diseases. Targeted microbiome transplant in atopic dermatitis. 2017. Available from: <https://clinicaltrials.gov/ct2/show/NCT03151148>. Accessed December 4, 2020.
24. Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, et al. First-in-human topical microbiome transplantation with *Roseomonas mucosa* for atopic dermatitis. *JCI Insight* 2018;3:e120608.
25. Myles IA, Castillo CR, Barbican KD, Kanakabandi K, Virtaneva K, Fitzmeyer E, et al. Therapeutic responses to *Roseomonas mucosa* in atopic dermatitis may involve lipid-mediated TNF-related epithelial repair. *Sci Transl Med* 2020;12:eaaz8631.
26. Jury CS, McHenry P, Burden AD, Lever R, Bilsland D. Narrowband ultraviolet B (UVB) phototherapy in children. *Clin Exp Dermatol* 2006;31:196-9.
27. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:327-49.
28. Clayton TH, Clark SM, Turner D, Goulden V. The treatment of severe atopic dermatitis in childhood with narrowband ultraviolet B phototherapy. *Clin Exp Dermatol* 2007;32:28-33.
29. Dayal S, Pathak K, Sahu P, Jain VK. Narrowband UV-B phototherapy in childhood atopic dermatitis: efficacy and safety. *An Bras Dermatol* 2017;92:801-6.
30. Simpson EL, Bruin-Weller M, Flohr C, Arden-Jones MR, Barbarot S, Deleuran M, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77:623-33.
31. Totri CR, Eichenfield LF, Logan K, Proudfoot L, Schmitt J, Lara-Corrales I, et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: the PeDRA TREAT survey. *J Am Acad Dermatol* 2017;76:281-5.
32. Proudfoot LE, Powell AM, Ayis S, Barbarot S, Baselga Torres E, Deleuran M, et al. The European TREATment of severe Atopic eczema in children Taskforce (TREAT) survey. *Br J Dermatol* 2013;169:901-9.
33. Paller AS, Siegfried EC, Vekeman F, Gadkari A, Kaur M, Mallya UG, et al. Treatment patterns of pediatric patients with atopic dermatitis: a claims data analysis. *J Am Acad Dermatol* 2020;82:651-60.
34. Drucker AM, Eyerich K, de Bruin-Weller MS, Thyssen JP, Spuls PI, Irvine AD, et al. Use of systemic corticosteroids for atopic dermatitis: International Eczema Council consensus statement. *Br J Dermatol* 2018;178:768-75.
35. Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema—a systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2007;21:606-19.
36. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013;172:351-6.
37. Anderson K, Putterman E, Rogers RS, Patel D, Treat JR, Castelo-Soccio L. Treatment of severe pediatric atopic dermatitis with methotrexate: a retrospective review. *Pediatr Dermatol* 2019;36:298-302.
38. Taieb Y, Baum S, Ben Amitai D, Barzilai A, Greenberger S. The use of methotrexate for treating childhood atopic dermatitis: a multicenter retrospective study. *J Dermatolog Treat* 2019;30:240-4.
39. Hon KL, Ching GK, Leung TF, Chow CM, Lee KK, Ng PC. Efficacy and tolerability at 3 and 6 months following use of azathioprine for recalcitrant atopic dermatitis in children and young adults. *J Dermatolog Treat* 2009;20:141-5.
40. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol* 2013;68:29-35.
41. Heller M, Shin HT, Orlov SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007;157:127-32.
42. Waxweiler WT, Agans R, Morrell DS. Systemic treatment of pediatric atopic dermatitis with azathioprine and mycophenolate mofetil. *Pediatr Dermatol* 2011;28:689-94.
43. Phan K, Smith SD. Mycophenolate mofetil and atopic dermatitis: systematic review and meta-analysis. *J Dermatolog Treat* 2020;31:810-4.
44. Agnihotri G, Shi K, Lio PA. A clinician's guide to the recognition and management of dupilumab-associated conjunctivitis. *Drugs R D* 2019;19:311-8.
45. Waldman RA, DeWane ME, Sloan B, Grant-Kels JM. Characterizing dupilumab facial redness: a multi-institution retrospective medical record review. *J Am Acad Dermatol* 2020;82:230-2.
46. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol* 2020;156:44-56.
47. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol* 2020;83:1282-93.
48. Cork MJ, Thaçi D, Eichenfield LF, Arkwright PD, Hultsch T, Davis JD, et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a phase IIa open-label trial and subsequent phase III open-label extension. *Br J Dermatol* 2020;182:85-96.
49. Silverberg JJ, Simpson EL, Thyssen JP, Gooderham M, Chan G, Feeney C, et al. Efficacy and safety of abrocitinib in patients with moderate-to-severe atopic dermatitis: a randomized clinical trial. *JAMA Dermatol* 2020;156:863-73.
50. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;145:877-84.
51. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol* 2020;183:242-55.
52. Kabashima K, Matsumura T, Komazaki H, Kawashima M, Nemolizumab-JP01 Study Group. Trial of nemolizumab and topical agents for atopic dermatitis with pruritus. *N Engl J Med* 2020;383:141-50.
53. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-32.
54. Marrs T, Perkin MR, Logan K, Craven J, Radulovic S, McLean WHI, et al. Bathing frequency is associated with skin barrier dysfunction and atopic dermatitis at three months of age. *J Allergy Clin Immunol Pract* 2020;8:2820-2.
55. Cardona ID, Kempe EE, Lary C, Ginder JH, Jain N. Frequent versus infrequent bathing in pediatric atopic dermatitis: a randomized clinical trial. *J Allergy Clin Immunol Pract* 2020;8:1014-21.
56. Maarouf M, Shi VY. Bleach for atopic dermatitis. *Dermatitis* 2018;29:120-6.
57. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. *J Allergy Clin Immunol* 2019;143:46-55.
58. Skjerven HO, Rehinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G, et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. *Lancet* 2020;395:951-61.

59. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ, et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. *Lancet* 2020;395:962-72.
60. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol* 2014;134:818-23.
61. Yamamoto-Hanada K, Kobayashi T, Williams HC, Mikami M, Saito-Abe M, Morita K, et al. Early aggressive intervention for infantile atopic dermatitis to prevent development of food allergy: a multicenter, investigator-blinded, randomized, parallel group controlled trial (PACI Study)—protocol for a randomized controlled trial. *Clin Transl Allergy* 2018;8:47.
62. Greer FR, Sicherer SH, Burks AW, Committee on Nutrition; Section on Allergy and Immunology. The effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, hydrolyzed formulas, and timing of introduction of allergenic complementary foods. *Pediatrics* 2019;143:e20190281.
63. Flohr C, Mann J. New approaches to the prevention of childhood atopic dermatitis. *Allergy* 2014;69:56-61.
64. Kantor R, Silverberg JI. Environmental risk factors and their role in the management of atopic dermatitis. *Expert Rev Clin Immunol* 2017;13:15-26.
65. Nankervis H, Pynn EV, Boyle RJ, Rushton L, Williams HC, Hewson DM, et al. House dust mite reduction and avoidance measures for treating eczema. *Cochrane Database Syst Rev* 2015;1:CD008426.
66. Eigenmann PA, Sicherer SH, Borkowski TA, Cohen BA, Sampson HA. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. *Pediatrics* 1998;101:E8.
67. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010;126:S1-58.
68. Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015;372:803-13.
69. Fleischer DM, Chan ES, Venter C, Spergel JM, Abrams EM, Stukus D, et al. A consensus approach to the primary prevention of food allergy through nutrition: guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. *J Allergy Clin Immunol Pract* 2021;9:22-43.e4.
70. Low DW, Jamil A, Md Nor N, Kader Ibrahim SB, Poh BK. Food restriction, nutrition status, and growth in toddlers with atopic dermatitis. *Pediatr Dermatol* 2020;37:69-77.
71. Nomura I, Katsunuma T, Tomikawa M, Shibata A, Kawahara H, Ohya Y, et al. Hypoproteinemia in severe childhood atopic dermatitis: a serious complication. *Pediatr Allergy Immunol* 2002;13:287-94.
72. Lack G. Epidemiologic risks for food allergy. *J Allergy Clin Immunol* 2008;121:1331-6.
73. Yoshida K, Kubo A, Fujita H, Yokouchi M, Ishii K, Kawasaki H, et al. Distinct behavior of human Langerhans cells and inflammatory dendritic epidermal cells at tight junctions in patients with atopic dermatitis. *J Allergy Clin Immunol* 2014;134:856-64.
74. Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int* 2018;67:24-31.
75. Fleischer DM, Bock SA, Spears GC, Wilson CG, Miyazawa NK, Gleason MC, et al. Oral food challenges in children with a diagnosis of food allergy. *J Pediatr* 2011;158:578-583.e1.
76. Roduit C, Frei R, Depner M, Karvonen AM, Renz H, Braun-Fahrlander C, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr* 2017;171:655-62.
77. Flohr C, Perkin M, Logan K, Marrs T, Radulovic S, Campbell LE, et al. Atopic dermatitis and disease severity are the main risk factors for food sensitization in exclusively breastfed infants. *J Invest Dermatol* 2014;134:345-50.
78. Tsakok T, Marrs T, Mohsin M, Baron S, du Toit G, Till S, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol* 2016;137:1071-8.
79. Shoda T, Futamura M, Yang L, Yamamoto-Hanada K, Narita M, Saito H, et al. Timing of eczema onset and risk of food allergy at 3 years of age: a hospital-based prospective birth cohort study. *J Dermatol Sci* 2016;84:144-8.
80. Miyaji Y, Yang L, Yamamoto-Hanada K, Narita M, Saito H, Ohya Y. Earlier aggressive treatment to shorten the duration of eczema in infants resulted in fewer food allergies at 2 years of age. *J Allergy Clin Immunol Pract* 2020;8:1721-1724.e6.
81. Natsume O, Kabashima S, Nakazato J, Yamamoto-Hanada K, Narita M, Kondo M, et al. Two-step egg introduction for prevention of egg allergy in high-risk infants with eczema (PETIT): a randomised, double-blind, placebo-controlled trial. *Lancet* 2017;389:276-86.