Article Type: From the Academy

Title: Guidelines of care for the management of atopic dermatitis in pediatric patients

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Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

Conflicts of Interest: Listed in text.

Supplementary files are available on:
Reprint Requests: No reprints available.

Manuscript word count: words [excluding abstract, references, figures, tables, appendix]
Abstract word count: 208
References:

Figures: 1
Online Supplementary figures: 0

Keywords: antihistamines, antimicrobials**,** atopic dermatitis, bathing, calcineurin inhibitors, corticosteroids, emollients, JAK inhibitor, topicals, wet wraps, phototherapy, methotrexate, cyclosporine, azathioprine, biologic, dupilumab

Publishable Conflict of Interest Statement

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

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Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Abstract

Background: Pediatric atopic dermatitis (AD) is a common, chronic inflammatory skin disorder that significantly impacts the quality of life of affected children and their families. Multiple therapies were approved to treat AD in children and adolescents since publication of the AAD's 2014 AD guidelines.

Objective: To provide evidence-based recommendations on the use of topical therapies, phototherapy, and systemic therapies for AD in children and adolescents.

Methods: A multidisciplinary workgroup conducted a systematic review and applied the GRADE approach for assessing the certainty of evidence and formulating and grading recommendations.

Results: The workgroup developed 19 evidence-based recommendations on the medical management of pediatric AD.

Limitations: This analysis is based on the best available evidence at the time it was conducted. Most randomized controlled trials of therapies for AD are of short duration limiting long-term efficacy and safety conclusions.

Conclusions: We make strong recommendations for the use of moisturizers, topical calcineurin inhibitors, topical corticosteroids, crisaborole ointment, roflumilast cream, ruxolitinib cream, tapinarof cream, dupilumab, tralokinumab, lebrikizumab, upadacitinib, abrocitinib, and baricitinib in the treatment of AD. We make conditional recommendations in favor of bathing, bleach baths, wet dressings, phototherapy, methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine. We conditionally recommend against the use of topical antimicrobials, PUVA phototherapy, and strongly recommend against systemic corticosteroids.

Abbreviations Used

AAD: American Academy of Dermatology

AD: Atopic dermatitis

AE: Adverse event

CDLQI: Children's Dermatology Life Quality Index

CI: Confidence interval

EASI: Eczema Area and Severity Index

FDA: Food and Drug Administration

HR: Hazard ratio

IGA: Investigator Global Assessment

JAKi: Janus kinase inhibitor

MD: Mean difference

MMF: mycophenolate mofetil

NB-UVB: Narrowband ultraviolet B

OR: Odds ratio

POEM: Patient Oriented Eczema Measure

PUVA: Psoralen plus ultraviolet A

QoL: Quality of life

RCT: Randomized controlled trial

RR: Risk ratio

SAE: Serious adverse event

SCORAD: Scoring of Atopic Dermatitis

TCI: Topical calcineurin inhibitor

TCS: Topical corticosteroids

UV: Ultraviolet

Scope and Objectives

The American Academy of Dermatology (AAD) recently published guidelines for the care of AD in adults, addressing: 1) phototherapy and systemic therapies, and 2) topical therapies.[1,2] While pediatric and adult AD share similarities, these guidelines recognize the unique safety, dosing, and patient-caregiver-provider interactions of individuals under the age of 18. The scope of the present guidelines focuses solely on pediatric AD (< 18 years of age).

Specifically, these guidelines provide evidence-based recommendations for topical therapies (prescription and non-prescription), phototherapy, and systemic therapies available in the United States. Children under 18 years of age with AD of any severity in any healthcare setting or context are the target population of these guidelines. Recommendations herein serve to update previously published guidelines.[3-6]

Topical therapies considered include non-prescription topical agents (e.g. moisturizers, bathing practices, and wet wraps) and pharmacologic topical modalities, including topical corticosteroids (TCS), topical calcineurin inhibitors (TCIs), Janus kinase inhibitors (JAKis), phosphodiesterase-4 (PDE-4) inhibitors, aryl hydrocarbon receptor agonists, antimicrobials and antihistamines. The use of ultraviolet (UV) B, UVA1, and psoralen plus UVA (PUVA) phototherapy is assessed. Systemic therapies evaluated include immunosuppressants, corticosteroids, antimetabolites, JAKis, interferon gamma, immunoglobulin, and monoclonal antibodies (biologics).

Methods

A multidisciplinary workgroup developed these guidelines using a systematic evidence review process, which included (i) identifying and prioritizing clinical questions and outcomes (**Table I**), (ii) systematic retrieval and assessment of evidence, and (iii) assessment of the certainty of the evidence and formulation of recommendations using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) (**Table II**).

Table I. Clinical questions and scope

Clinical Questions		
1. What are the efficacy and safety of topical therapies for the management of AD in children and adolescents?		
2. What are the efficacy and safety of phototherapy or photochemotherapy for the treatment of AD in children and adolescents?		
3. What are the efficacy and safety of systemic therapies for the treatment of AD in children and adolescents?		
Outcomes of interest for therapy questions		
Efficacy Outcomes	Change in clinical signs/symptoms of disease as assessed by a clinician	
	Prevention of flares	
Patient-Reported Outcomes	Change in patient-reported signs/symptoms	
	Change in quality of life	
	Change in itch severity	
Safety Outcomes	Serious adverse events	
	Withdrawal due to adverse events	
	Infection	
Scope for therapy questions		
Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Population	Children & adolescents (< 18 years of age) with a clinical diagnosis of AD (including "eczema" or "atopic eczema")	Immunocompromised patients, contact dermatitis, seborrheic dermatitis, varicose eczema, discoid eczema; infected atopic dermatitis
Intervention	Topical, systemic, or phototherapy/photochemotherapy interventions available and approved for use (for any indication) in the US	Treatments not available or approved for use (for any indication) in the US
Study Design	Published RCTs in which study participants are investigated (inter-individual, parallel-arm trials)	Unpublished research, observational studies, case series, case reports, modeling studies, narrative reviews

Existing, current, high-quality, relevant systematic reviews were identified via a systematic search, including a systematic review of bleach baths[7], two systematic reviews and network meta-analyses on topical treatments[8,9], and a living systematic review and network meta-analysis of systemic immunomodulatory treatments for AD[10]. If relevant systematic reviews were not available, they were conducted de novo by the workgroup and AAD staff.

Table II. Strength of recommendation and certainty of evidence

Strength of Recommendation	Wording	Implication[11-13]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risks and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; the recommendation applies to most patients in most circumstances.
Good Practice Statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[13]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burdens; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"We conditionally recommend against…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Certainty of Evidence	**Wording**	**Implication[11,12]**
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low certainty evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

For detailed methodology, see **Supplemental Appendix 1**.

Definition

AD, also known as atopic eczema, is a chronic, pruritic inflammatory skin disease that occurs with highest prevalence in children. It follows a relapsing course. AD is often associated with a personal or family history of atopy.

MEDICAL MANAGEMENT

Reducing symptoms, specifically dermatitis and pruritus, and minimizing therapeutic risks, while enhancing QoL for patients and their caregivers, are key goals of pediatric AD management. To

realize these goals, a variety of nonpharmacologic and pharmacologic therapies are available and evaluated in these guidelines.

The age ranges included in the clinical practice recommendations for the management of pediatric AD reflect FDA approvals and the ages of patients studied in clinical trials for the recommended therapies. These parameters provide a regulatory and evidence-based framework for treatment guidance. However, due to the inherent limitations of pediatric clinical research—including ethical considerations, smaller patient populations, and challenges in trial design—many effective therapies have not been formally studied or approved in younger age groups. Consequently, in real-world pediatric dermatology practice, clinicians frequently use medications off-label, guided by the totality of evidence, clinical experience, and individual patient needs. This approach is essential to ensure timely and effective care for children across all age groups, even when formal approvals are lacking (**Figure 1 and Table V**).

Figure 1. Treatment algorithm for children and adolescents with atopic dermatitis. *FDA*, U.S. Food and Drug Administration, *QoL*, Quality of life. **Disclaimer:** Age ranges reflect FDA indication and/or ages of patients studied in clinical trials. Many therapies with demonstrated efficacy and safety in older children or adults are commonly used off-label in pediatric dermatology practice. Such use is guided by clinical judgment, available literature, and the need to provide effective, individualized care despite the absence of formal regulatory approval for certain age groups.

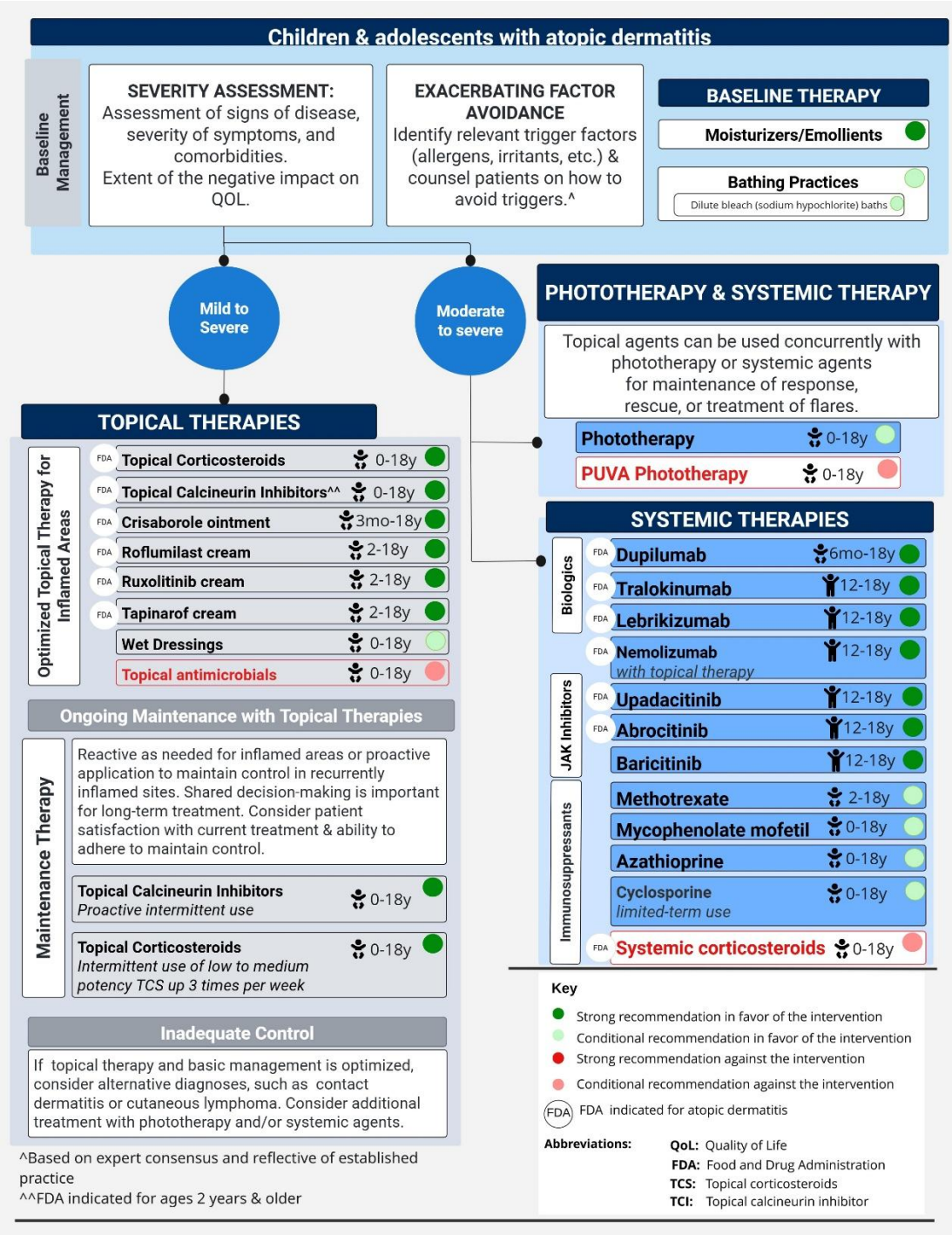

Table V. Recommendations for the medical management of atopic dermatitis in children and adolescents. AD: atopic dermatitis; FDA: Food and Drug Administration; PUVA: psoralen plus ultraviolet A; SCC: squamous cell carcinoma

Recommendation	Strength	Certainty of Evidence	Evidence
Nonprescription topical interventions			
For pediatric patients up to age 18 with AD, we recommend the use of moisturizers. Remark: The use of a particular moisturizer, vehicle, or active ingredient cannot be recommended based on the available evidence.	Strong	Moderate	14-38
For pediatric patients up to age 18 with AD, we conditionally recommend bathing for treatment and maintenance. Remark: A standard for the frequency or duration of bathing appropriate for individuals with AD cannot be established based on the current available evidence.	Conditional	Very low	39-42
For pediatric patients up to age 18 with AD, we conditionally recommend dilute bleach (sodium hypochlorite) baths under the guidance of a healthcare professional skilled in the management of AD.	Conditional	Very low	7
For pediatric patients up to age 18 with AD, we conditionally recommend the use of wet dressings under the guidance of a health care professional skilled in the management of AD. Remark: The addition of wet dressings with topical corticosteroids is typically encouraged during AD flares rather than as maintenance therapy. Evidence is not available for the optimal method of wet dressing therapy.	Conditional	Low	43
Topical antimicrobials			
We conditionally recommend *against* the use of topical antimicrobials for AD without signs of infection in pediatric patients up to the age of 18.	Conditional	Very low	8,44
Topical calcineurin inhibitors			
For pediatric patients up to the age of 18, we recommend the use of topical calcineurin inhibitors (tacrolimus, pimecrolimus).	Strong	Moderate	45-61
For pediatric patients up to the age of 18, we recommend proactive use of intermittent TCIs as maintenance therapy.	Strong	Moderate	55,61-68
Topical corticosteroids			
For pediatric patients up to age 18 with AD, we recommend topical corticosteroids.	Strong	Moderate	32,58,59,69-77
For pediatric patients up to age 18 with AD, we recommend intermittent use of low to medium potency topical corticosteroids as maintenance therapy (up to 3 times per week).	Strong	Moderate	26,78,79
Topical phosphodiesterase-4 inhibitors			
For pediatric patients 3 months and older with mild-to-moderate AD, we recommend the use of crisaborole.	Strong	Moderate	59,80-87
For pediatric patients aged 2 years and older with mild-to-moderate AD, we recommend the use of roflumilast 0.15% cream.	Strong	Moderate	88,89
Topical Janus kinase inhibitors			
For pediatric patients aged 2 years and older with AD, we recommend ruxolitinib cream.	Strong	Moderate	90
Topical aryl hydrocarbon receptor agonists			

For pediatric patients aged 2 years and older with AD, we recommend tapinarof cream.	Strong	High	91-93
Phototherapy			
For pediatric patients up to age 18 with AD, we conditionally recommend phototherapy	Conditional	Low	94,95
For pediatric patients up to age 18 with AD, we conditionally recommend *against* PUVA phototherapy *Remark:* PUVA phototherapy should be avoided if other modalities are available given the recognized long-term safety effects, specifically the increased risk of UV-induced SCCs and photoaging.	Conditional	Very low	95
Monoclonal antibodies (biologics)			
For pediatric patients 6 months and older with moderate to severe AD, we recommend dupilumab *Remarks*: There is less efficacy and safety data on children aged 6 months to < 2 years.	Strong	Moderate	96-99
For pediatric patients 12 years and older with moderate to severe AD, we recommend tralokinumab	Strong	Moderate	100
For pediatric patients 12 years and older with moderate to severe AD, we recommend lebrikizumab	Strong	Moderate	101-103
For pediatric patients 12 years and older with moderate-to-severe AD, we recommend nemolizumab with concomitant topical therapy	Strong	Moderate	104,105
JAK inhibitors			
For pediatric patients 12 years and older with moderate to severe AD, we recommend upadacitinib *Remarks:* Upadacitinib is approved by the FDA in patients aged 12 and older with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable.	Strong	Moderate	106-110
For pediatric patients 12 years and older with moderate to severe AD, we recommend abrocitinib *Remark:* Abrocitinib is approved by the FDA in patients aged 12 and older with AD who have failed other systemic therapies (pills or injections, including biologics) or when use of those therapies is inadvisable.	Strong	Moderate	111-115
For pediatric patients 12 years and older with moderate to severe AD, we recommend baricitinib *Remark:* Baricitinib is not approved by the FDA for use in AD, but is approved by the European Medicines Agency for ages 2 years and older.	Strong	Moderate	116
Immunosuppressants			
For pediatric patients 2 years and older with moderate to severe AD, we conditionally recommend methotrexate with proper monitoring *Remarks:* Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients. In the US, the FDA has not approved methotrexate for use in AD.	Conditional	Low	117,118
For pediatric patients up to 18 years with refractory moderate to severe AD, we conditionally recommend mycophenolate mofetil^ with proper monitoring *Remarks:* Mycophenolate mofetil is not approved by the FDA for use in AD. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Very low	119,120
For pediatric patients up to 18 years with refractory moderate to severe AD, we conditionally recommend limited-term use of azathioprine with proper monitoring and prescreening of thiopurine methyltransferase activity	Conditional	Very low	121,122

Remark: Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.			
For pediatric patients up to 18 years with refractory moderate to severe AD, we conditionally recommend limited-term use of cyclosporine with proper monitoring *Remarks:* The FDA has not approved cyclosporine for use in AD. The FDA has approved limited-term use (up to one year) in psoriasis. Comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.	Conditional	Low	123-127
For pediatric patients up to 18 years with AD, we recommend *against* systemic corticosteroids *Remarks:* Their use should be reserved exclusively for acute, severe exacerbations and as a short-term bridge therapy for other systemic, corticosteroid-sparing therapy. Systemic corticosteroids should not be used as maintenance therapy.	Good Practice Statement		

^mycophenolic acid can be used interchangeably depending on availability. Note that dosing differs for mycophenolic acid and mycophenolate mofetil.

TOPICAL THERAPIES

Optimal use of topical therapies is a cornerstone of AD management as these therapies are generally effective, and lower risk than systemic therapies. However, efficacy is dependent on consistency and appropriate usage/dosing (**Table VI**).

Table VI. Medication dosing table for use in children and adolescents. *bid*, twice daily, *qd*, once daily, *wk*, week, *FDA*, U.S. Food and Drug Administration, *mo*, month, *SC*, subcutaneous, *PO*, by mouth

Medication (age of indication)	**Dose**	**Notes**
Tacrolimus ointment 0.03% (≥2 years)	bid to affected skin	Reassess at 6 weeks; Do not use with occlusive dressing
Tacrolimus ointment 0.1% (≥16 years)	Bid to affected skin	Studies have demonstrated safety in children 2 years and older, despite lack of FDA approval in this age group[48,128-135]; Do not use occlusive dressing
Pimecrolimus cream 1% (≥2 years)	bid to affected skin	Reassess at 6 weeks; Do not use with occlusive dressing
Crisaborole ointment 2% (≥ 3 months)	bid to affected skin	Once clinical effect is achieved consider reducing application to qd
Roflumilast cream 0.15% (≥2 years)	qd to affected skin	
Ruxolitinib cream 1.5% (≥2 years)	bid to affected skin; maximum of 60g/wk, 100g/2wk	Treatment area should not exceed 20% BSA; reassess at 24wks
Tapinarof cream 1% (≥ 2 years)	qd to affected skin^	FDA-approved for plaque psoriasis in adults
Topical corticosteroids	Qd to bid for flares; maintenance therapy may involve up to 3 times per week application; Use fingertip unit (FTU) guidance; avoid overuse to prevent skin thinning	Infants and young children have higher absorption; prefer low-potency steroids and limit duration; Use low-potency steroids for the face and intertriginous areas; medium potency (e.g., triamcinolone 0.1%) for the body; high-potency only for severe flares and short durations
Dupilumab (≥ 3 months)	6mo-5y, 5-14kg 200mg SC q4wk 6mo-5y, 15-29kg 300mg SC q4wk 6-17y, 15-29kg 600 mg SC x1 on day 1, then 300 mg SC q4wk 6-17y, 30-59kg 400 mg SC x1 on day 1, then 200 mg SC q2wk 6-17y, >60kg 600 mg SC x1 on day 1, then 300 mg SC	
Tralokinumab (≥12 years)	300mg SC x1 on day 1, then 150mg SC q2wk	
Lebrikizumab (≥12 years)	500 mg SC x1 on wk 0, 2, then 250 mg SC q2wk	Dose specified for individuals >40kg; If adequate clinical

		response at 16 wks consider once monthly dosing
Nemolizumab (≥12 years)	60 mg SC x1 on day 1, then 30 mg SC q4wk	Concomitant use of optimized prescription topical therapy is recommended; After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a dosage of 30 mg q8wk is recommended
Upadacitinib (≥12 years)	15 or 30 mg PO qd	Dose specified for individuals >40kg; may increase to 30 mg PO qd if inadequate response
Abrocitinib (≥12 years)	100 or 200 mg PO qd	Dose specified for individuals >25kg; Start with 100 mg PO qd, increase to 200 mg PO qd if needed; use lowest effective dose
Baricitinib (Off-label)	2mg or 4mg PO qd^	Approved for use for AD in adults and children ≥ 2 years of age in Europe
Methotrexate (Off-label)	10-15mg PO or SC weekly^^	Once control is achieved, lower dose to lowest possible effective dose. Despite broad usage, there is a lack of consensus on dosing for AD. Folic acid supplementation recommended to reduce side effects.
Mycophenolate mofetil (Off-label)	Up to 3000mg PO daily, divided BID	Mycophenolate mofetil oral products are not interchangeable w/ mycophenolic acid DR products; do not substitute on a mg-to-mg basis
Azathioprine (Off-label)	2 to 3.5 mg/kg PO daily in patients with normal levels of thiopurine methyltransferase^	Thiopurine methyltransferase genotype or enzyme activity should be checked before treatment initiation and the dose lowered, or the medication not started, depending on the results.
Cyclosporine (Off-label)	2.5 to 5 mg/kg PO daily^	Start at the higher end of dosing range and decrease once control is achieved. Use is generally limited to 1 year. Prescribers should be aware of whether the modified or non-modified form of cyclosporine is being dispensed as this can alter bioavailability, efficacy, and safety.

^ Based on dosing in clinical trials of the management of AD in children and/or adolescents

^^Based on dosing recommendations in 18 dermatological guidelines with explicit consideration of the dosing regimen of MTX for AD in children.[136]

Non-prescription therapies

Moisturizers

The workgroup strongly recommends the use of moisturizers in AD but cannot recommend the use of a particular moisturizer, vehicle, or active ingredient based on the available evidence. (**Supplemental Table 1**).

Analysis of nine RCTs (1,260 pediatric AD patients) found moisturizers reduce AD disease severity as assessed by Eczema Area Severity Index (EASI), Scoring of Atopic Dermatitis (SCORAD), and Total Symptom Score.[15-17,20-22,25,30,33] Three RCTs (216 patients) found patients receiving moisturizer were more likely to achieve Investigator Global Assessment (IGA) 0 (clear) or IGA 1 (almost clear) over a follow-up period ranging from three to six weeks.[16,19,30] Serious adverse events (SAEs) were rare, and moisturizers resulted in little to no difference in the number of participants experiencing an AE or discontinuing treatment due to AEs.[14,16,17,19,20,22,25,28,30,33,37]

The use of moisturizers with TCS twice daily for three weeks does not appear to offer greater clinical improvement (SCORAD or Mean Global Condition Score) or improvement in QoL than TCS twice daily alone (**Supplemental Table 2**). [27,29] Moisturizer alone may result in a decrease in the number of clear or almost clear patients (IGA 0 or 1),[23] and an increase in the number of participants experiencing a flare.[26,31,35] However, in three four-week RCTs, after treatment and stabilization of mild-to-moderate AD with 4 weeks of TCS, moisturizer alone (compared to moisturizer + TCS) achieved a similar mean SCORAD reduction, and similar Patient Oriented Eczema Measure (POEM),[31] itch[32], and QoL scores as TCS alone.[26]. However, in three four-

week RCTs, moisturizer alone achieved a similar mean SCORAD reduction, and similar Patient Oriented Eczema Measure (POEM),[31] itch[32], and QoL scores as TCS alone.[26](**Supplemental Table 3**).[18,31,36]. Overall, adverse events and discontinuation were rare across the moisturizer-only and TCS and moisturizer treatment groups.[18,23,24,26,31,35]

Of all non-prescription interventions, moisturizers have the strongest evidence, while also safe, affordable, and accessible. Public perception and support of moisturizers and particular active ingredients improve patient and caregiver engagement and compliance. Although allergenicity is always a theoretical risk (particularly for AD patients), there are numerous hypoallergenic products available. It may be prudent to caution caregivers to avoid moisturizers with many additives (particularly plant-based additives which may be sensitizers).

Bathing practices

While bathing can be laborious for patients and families, the available data suggest it is safe, inexpensive, and reduces social stigma. That said, there is limited evidence of the efficacy of bathing in patients with AD compared to not bathing, or bathing with or without soap (**Supplemental Tables 4-5**). In one study of 58 pediatric AD patients, washing with soap resulted in little difference in EASI or POEM scores.[40] Another small study found no difference in daily bathing versus twice weekly bathing in children with AD.[41] Thus, we conditionally recommend bathing for treatment and maintenance for pediatric patients with AD, but we cannot recommend a standard frequency or duration of bathing based on the paucity of data. In AD patients, it may be advisable to use a hypoallergenic cleanser designed for sensitive skin.

A 16-week RCT of 461 patients found bath additives result in little to no difference in POEM score or QoL and may increase AEs slightly (**Supplemental Table 6**).[42] Emollient use after bathing is a standard practice among providers caring for AD patients. An RCT of 84 patients found twice daily soak and seal baths (15-20 minutes) resulted in a larger SCORAD reduction than twice weekly soak and seal baths (10 minutes or less) (**Supplemental Table 7**).[39] Quality of life, as assessed by patients and caregivers, did not differ meaningfully between groups.

Bleach baths

For pediatric AD patients, we conditionally recommend dilute bleach (sodium hypochlorite) baths under the guidance of a healthcare professional skilled in AD management. The data are limited with serious imprecision given the small sample sizes of the included studies. (**Supplemental Table 8**).

Meta-analysis of eight RCTs including unpublished data found bleach baths may improve clinician rating of AD severity (EASI) possibly by reducing *Staphylococcus* colonization and/or increasing microbial flora diversity, but seems to have minimal impact on POEM score, itch response, and QoL.[7] Bleach baths were found to be safe with few, if any, AEs. Diluting the bleach is important as bleach alone can be caustic, causing burns, itch, and dryness. In sum, bleach baths are low-risk, readily accessible, and inexpensive. Two important points to consider: 1) bleach bathing appears to reduce *Staphylococcus* colonization but its effect on infection is less clear, and 2) a plain water bath may not be less advantageous than a bleach bath.[137 138,139]

Wet wrap therapy

The workgroup conditionally recommends use of wet dressings under the guidance of a healthcare professional skilled in the management of AD (**Supplemental Table 9**). The addition of wet dressings with TCS is typically encouraged during AD flares, rather than as maintenance therapy.

Hindley et al., the only included study, is specific to the inpatient setting.[43] The experimental group in this study received one week of wet wraps applied daily for 24 hours over 1% hydrocortisone ointment (and if necessary, more potent topical steroids), followed by wet wraps for 12 or 24 hours a day depending on progress; the control group received conventional AD treatment (regular use of emollients applied at least three times a day; 1% hydrocortisone ointment applied twice daily and use of more potent topical steroids if necessary). Wet wrap therapy resulted in little to no difference in the mean SCORAD score. However, wet wrap therapy was used for maintenance rather than flares (where they would probably be more effective), and the control group still used treatments as needed. Other limitaitons include the limited age range of patients, and the fact that children in this age group are often fully clothed, such that clothing provides a partial dressing *de facto*.

Wet wrap therapy can be labor- and time-intensive for caregivers, and prolonged or continuous use may limit daily activities for patients. Therapy considerations include steroid potency (wet dressings can potentiate TCS), temperature control, and overall safety. It is important to consider infant-specific safety issues (dressing in layered pajamas may result in strangulation, hypothermia, etc.), skin maceration, and discomfort. Moreover, evidence is not available for the optimal method of wet dressing therapy.

Topical calcineurin inhibitors

Topical calcineurin inhibitors are a mainstay in pediatric AD treatment due to their favorable safety profile and lack of atrophy as a possible side effect. Tacrolimus ointment topically comes in 0.03% and 0.1% strengths, while pimecrolimus cream comes as a 1% formulation. Topical calcineurin inhibitors can be effective for both AD flares and intermittently as maintenance therapy (**Supplemental Tables 9-15**).

Tacrolimus

Two RCTs (3-12 weeks) with over 300 children with moderate-to-severe AD demonstrated tacrolimus 0.1% ointment probably meaningfully increases the number of participants cleared or with excellent improvement-256 more patients per 1,000 (95%CI from 27 fewer to 1,000 more) compared to placebo- while also resulting in a clinically meaningful reduction in itch and low discontinuation rate.[45,48] Data on tacrolimus 0.03% ointment are similar in terms of efficacy and itch response, with low incidence of AEs. Events of interest included herpes simplex and stinging/burning.[45,46,48,49] Furthermore, tacrolimus use is unlikely to increase the risk of cancer in pediatric or adult AD patients, based on 64 non-randomized studies.[47] Of note, there do not appear to be additional risks, other than local effects, in children applying tacrolimus 0.1% ointment compared to those applying 0.03% ointment.[48,128-135]

TCIs may also be used for AD maintenance therapy. In a study of tacrolimus 0.03% ointment twice weekly proactively for 12 months versus vehicle in children aged 2-15 years with mild-to-severe AD, use of tacrolimus reduced the number of individuals experiencing a flare (RR 0.70 [95% CI 0.57 to 0.87]); serious adverse events were rare and AEs similar between groups.[62]

Pruritus and impetigo were reported more often with tacrolimus, but herpes simplex rates were comparable.

Pimecrolimus

Pooling data from eight RCTs (2,637 patients) comparing pimecrolimus 1% twice daily for 2 to 14 weeks to vehicle in mild-to-moderate AD patients aged 3 months to 17 years demonstrates significantly more patients using pimecrolimus achieved IGA 0/1 (RR 1.87 [95% CI 1.33 to 2.61]).[50,51,53-55,58,60,61] Furthermore, in four RCTs, significantly more patients achieved no to mild itch following pimecrolimus treatment.[51,53-55] From a safety standpoint, pimecrolimus resulted in little to no difference in SAEs, withdrawals due to AEs were rare and comparable across treatment groups, and application site burning occurred at a similar rate across treatment groups.[54,58 51,52,56]

Pimecrolimus 1% cream is effective and safe for long-term (24-52 weeks) use as well. Four RCTs (1,689 patients) demonstrated long-term use of pimecrolimus reduces AD exacerbations (RR 1.65 [95% CI 1.47 to 1.85]).[61,65,67] Long-term pimecrolimus use may also increase the number of patients achieving IGA 0/1 and no or mild itch while reducing SAEs and withdrawals due to AEs.[61,63,65-68]

TCI use in children under two years of age

While Food and Drug Administration (FDA) approval of TCIs (both tacrolimus and pimecrolimus) is for ages 2 years and over, their use in children under 2 years is supported by several nonrandomized and clinical studies (**Supplemental Table 15**); other countries have approved use in children as young as 3 months. Burning and stinging are documented side

effects, and application site reactions may limit use – this may occur more with tacrolimus than pimecrolimus. The boxed warning on TCIs may also pose a potential concern for caregivers; providers should discuss that while the medications carry a boxed warning of cancer, the warning is based on theoretical risks from high-dose systemic calcineurin inhibitors used in post-transplant patients, and there is no evidence of a causal relationship between TCIs and malignancy.[47,140-142] In 2021, Health Canada removed the boxed warning of a potential association of TCIs and malignancy following a review of current data, including two large, long-term, post-authorization safety studies, which indicate no evidence of an increased rate of lymphoma with the use of TCIs.[143,144]

Topical Corticosteroids

Topical corticosteroids are a mainstay of AD treatment in children and adults, and the evidence supports a recommendation in favor of their use for the management of AD in children and adolescents (**Supplemental Tables 16-21**). They have the longest track record of any FDA-approved pediatric AD treatment and are safe and effective when used appropriately. While concerns about side effects, particularly atrophy, are valid, TCS are commonly considered first-line in most cases due to affordability and accessibility. Anatomical site is an important consideration when selecting a TCS potency (i.e. using lower potency agents on the face, neck, genitals, and body folds). While some dermatologists prefer high and very high potency steroids (at least initially) to control active disease, others use the lowest potency agent needed for the situation and increase potency if needed (**Table VII**).

Table VII. Relative potencies of topical corticosteroids. Reprinted with permission from: Paller and Mancini.[145] Copyright 2011 Elsevier. Includes representative examples and not all available agents.

Class	Drug	Dosage form(s)	Strength (%)
I. Very high potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
II. High potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
III-IV. Medium potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamicnolone acetonide	Cream, ointment	0.1
V. Lower-medium potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
VI. Low potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
VII. Lowest potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

High potency and very high potency topical steroids

Higher rates of AEs are associated with higher potency TCS – while atrophy is the most discussed, hypothalamic-pituitary-adrenal axis suppression is also a consideration. Nevertheless, high-potency TCS can be extremely effective in rapidly controlling flares and may be a good

option in older children. In adolescents (aged 12-17 years) with moderate-to-severe AD, compared to placebo, clobetasol propionate 0.05% foam twice daily for two weeks resulted in a large increase in the proportion of patients achieving an IGA of 0 or 1 (RR 5.87 [95% CI1.96 to 17.61]), but increased treatment-emergent AEs slightly (RR 1.39 [95% CI 0.30 to 6.52]).[69]

Medium potency topical steroids and maintenance therapy

Medium-potency TCS are an effective, safer alternative to high-potency TCS. In children aged 1 to 12 months with infantile facial AD (n=36), mometasone furoate 0.1% cream twice daily for 10 days was found to be safe with a side effect profile similar to vehicle, and resulted in a greater improvement in EASI scores, itch response and QoL.[70] Similar safety and efficacy were reported with fluticasone propionate 0.05% cream twice daily for 4 weeks in children and adolescents (aged 6 months to 18 years) with moderate-to-severe AD.[32]

Medium potency TCS are also recommended for maintenance therapy (**Table V**). Maintenance therapy aims to reduce flares and relapse while minimizing AEs from overuse of TCS. In studies ranging from 16 to 20 weeks in patients as young as 1 year of age, fluticasone propionate 0.05% cream daily twice per week reduced SCORAD and disease exacerbations (RR 0.36 [95% CI 0.12 to 1.15]), and had a safety and discontinuation profile similar to the emollient comparator (**Supplemental Table 19**).[26,78,79]

Lower medium potency and low potency topical steroids

While high-potency and medium-potency TCS work quickly, they may increase AEs, particularly in younger pediatric patients. For these patients as well as those with mild AD, lower medium potency and low potency TCS can be an effective option.

In several studies, hydrocortisone butyrate 0.1% cream twice daily for 4 weeks in patients ranging from 3 months to 18 years was effective in reducing EASI and itch, with rare SAEs and discontinuation.[59,71,73] Additionally, fluticasone 0.05% cream twice weekly for 16 weeks reduced AD exacerbations (RR 0.19 [95% CI 0.11 to 0.35]).[72] Even weaker steroids such as hydrocortisone 1%, fluocinolone 0.01%, and desonide 0.05% applied twice daily to affected skin can be effective in milder cases and younger patients. In patients with mild disease, low-potency steroids can significantly reduce SCORAD, itch, and flares with fewer AEs than higher-potency TCS.[58,74-77]

Adverse effects and monitoring

Many caregivers and patients may be afraid to use TCS, and many providers may be fearful of potential cutaneous and systemic AEs. A systematic review and patient panel found patients with AD value non-corticosteroid therapies. When using TCS, they prefer to use the medications for the minimum amount of time possible and place a high value on rapidly relieving itch.[146] Using a Likert scale to document TCS concerns, AD patients and caregivers ranked their distress level a 6.5/10 on average (with 10 as the highest level of distress/concern).[147]

When used appropriately, TCS are safe and effective. It is important to keep in mind the patient's age, disease severity, body surface area, and steroid potency. Appropriate treatment may require using a moderate or high potency steroid for several weeks. In patients with frequently relapsing disease, lower and medium potency TCS can be used as maintenance therapy up to three times per week to help reduce disease flares and increase comfort.

Topical antimicrobials

Antimicrobials

Topical antimicrobials are often requested due to concern of infection or the impression they are a standard of care. Moreover, many non-dermatologists prescribe topical antimicrobials (or recommend non-prescription antimicrobial products) for use on AD skin. The workgroup conditionally recommends against the use of topical antimicrobials (antifungals and antibiotics) for AD without signs of infection in pediatric patients (**Table V**).

Our recommendation focuses on uninfected skin, which is different than infected skin (i.e., with overt impetiginization or cellulitis) that would clearly benefit from antimicrobial therapy. There are limited data on this topic, and there are concerns about antimicrobial stewardship and contact allergen sensitivity development risk, particularly on the impaired skin barrier in AD. Additionally, body surface area is an important consideration in deciding whether to treat with topical antimicrobials or systemic antibiotics.

While there is no direct pediatric-specific evidence to assess the efficacy and safety of topical antibiotics for uninfected AD, a systematic review suggests topical antibiotic use likely results in no meaningful difference from control in SCORAD, itch score, rate of flares, and QoL in individuals of any age with uninfected AD (**Supplemental Table 22**).[8] Specific to topical antifungals, in a study of 29 pediatric AD patients, hydrocortisone 1% plus miconazole cream twice daily for 2 weeks did not outperform hydrocortisone 1% cream alone twice daily for two weeks in terms of investigator- or patient-assessed response (**Supplemental Table 23**).[44]

Topical phosphodiesterase inhibitors

Crisaborole

Crisaborole, a phosphodiesterase-4 inhibitor, is a safe and effective non-steroidal treatment option for AD patients 3 months and older (**Supplemental Table 24**). In clinical trials, crisaborole reduced EASI scores (mean % change -26.62), POEM scores, and itch, and resulted in more patients achieving IGA 0 or 1 (RR 1.53 [95% CI 1.25 to 1.87]).[59,82-84] Daily, long-term (52 weeks) use decreased flares (p = 0.0042) and increased flare-free maintenance (p = 0.0034), without safety concerns beyond those seen in shorter-term trials.[80] Crisaborole resulted in little to no difference in discontinuation vs vehicle and no SAEs were reported across groups in clinical trials.[82,83] However treatment-related AEs appear to be more common with crisaborole, particularly application site pain.[82,83] Tolerance is a critical issue, particularly as application site burning and stinging are documented side effects and application site reactions may limit use.[86,148,149]

Roflumilast

Roflumilast is another phosphodiesterase-4 inhibitor. The workgroup recommends the use of roflumilast 0.15% cream for children aged 2 years and older with mild-to-moderate AD (**Table V**). Three RCTs found significantly more patients achieved EASI 75 (RR 2.06 [95% CI 1.70 to 2.49]) and IGA 0 or 1 using roflumilast daily for 28 days compared to vehicle and roflumilast use increased the number of patients achieving clinically meaningful itch reduction (**Supplemental Table 25**).[88,89] Discontinuation was rare, with similar rates between groups, and the rates of treatment-emergent AEs of interest were not meaningfully higher in participants receiving roflumilast.[88,89] Roflumilast may not have the same degree of application site pain and burning as

crisaborole. Interestingly, in a 52-week open-label extension, proactive treatment of roflumilast (twice weekly application to normal-appearing flare-prone sites) maintained improvement in AD signs and symptoms; this use of the medication may keep skin clearer in a more consistent manner than the current practice of reactive treatment.[150]

Topical JAK inhibitors

Currently, ruxolitinib is approved for pediatric patients aged 2 years and older whose disease is not adequately controlled with other topical prescription therapies, or when those therapies are not advisable. However, new trial data indicate safety and efficacy in children as young as 2 years old and FDA approval for younger AD patients is imminent. In two large RCTs, ruxolitinib 1.5% cream twice daily for 8 weeks reduced EASI scores, resulted in a large increase in the proportion of patients achieving IGA 0 or 1, and increased the number of patients achieving a meaningful itch response compared with vehicle (**Supplemental Table 26**).[90] Furthermore, in a large meta-analysis of topical anti-inflammatory treatments for eczema in adults and children, ruxolitinib was similar in efficacy to potent topical steroids (i.e. betamethasone valerate 0.1%, betamethasone dipropionate 0.05%), and tacrolimus 0.1%.[151] Serious adverse events and withdrawal due to AEs are uncommon with rates similar to those of patients receiving vehicle. Furthermore, uncontrolled long-term data (52 weeks) indicate ruxolitinib maintains disease control while continuing to be safe with few treatment-related AEs.[152]

Topical ruxolitinib carries a boxed warning based on adverse events reported with the oral JAK inhibitor tofacitinib (serious side effects – infections, blood clots, cancer, and heart disease). While topical ruxolitinib appears to be safe, other options should be considered first in patients

with risk factors for serious infections, cancer, thrombosis, or cardiovascular events. Suggested use is limited to 20% body surface area due to the bioavailability and systemic absorption concerns.

Topical aryl hydrocarbon receptor agonist

Tapinarof is a first-in-class topical aryl hydrocarbon receptor agonist approved for patients aged 2 years and older with moderate-to-severe AD. Pediatric-specific evidence aligned with our inclusion criteria was not available. However, the ADORING trials included patients aged 2 years and older, and over 80% of the participants were children.[93] Additional data (particularly relating to AEs) were derived from a trial of 12 to 65 year olds (13% of the study population was between 12 and 17 years of age) (**Supplemental Table 27**).[92]

In the ADORING trials, tapinarof increased the number of patients achieving EASI75 (RR 2.60 [95% CI 2.06 to 3.29]), a meaningful itch response (RR = 1.77 [95% CI 1.43 to 2.19]), and a meaningful vIGA-AD response (RR 2.89 [95% CI 2.16 to 3.86]) compared to vehicle.[93] Although SAEs, were rare and rates of withdrawal due to AEs were similar between groups, tapinarof increased treatment-related AEs slightly.[92,93] Follicular cutaneous AEs (e.g. folliculitis, acneiform lesion) can occur and should be discussed when prescribing.

PHOTOTHERAPY

While phototherapy is an effective and safe method to treat severe cases of AD involving many body sites, it can be time-consuming as patients typically have to receive treatment two to three times a week at a dermatology office (though home phototherapy unites can improve

607 convenience). The workgroup conditionally recommended phototherapy due to low-certainty
608 evidence (**Table V**).
609
610 A Cochrane systematic review conducted in 2021 was updated to identify new pediatric-specific
611 evidence.[95] The review identified nine studies including children, adolescents, and adults.
612 However, pediatric-specific data were not reported in any of the studies. An additional pediatric
613 split-body study of 12 AD patients compared narrowband ultraviolet B (NB-UVB) combined
614 with 1% pimecrolimus cream with 1% pimecrolimus cream alone – the side treated with NB-
615 UVB had a mean reduction of 56% in EASI vs 54% with no treatment; bias in this study was
616 moderate due to minimal methods, analysis, and outcome reporting.[94]
617
618 We conditionally recommend against PUVA because, while evidence is not available, the safety
619 risks are higher and include various skin cancers, particularly squamous cell carcinoma (**Table**
620 **V**). This recommendation applies only to UVA combined with a psoralen-based treatment and is
621 not a recommendation against UVA light alone.
622
623 **SYSTEMIC THERAPIES**
624 For children and adolescents for whom optimal topical management is insufficient to
625 achieve AD control or who have more severe, widespread AD, or with substantially impaired
626 QoL, systemic therapies may be required to achieve management goals. Shared decision-making
627 is essential when initiating these advanced therapies, considering the severity of AD, its impact
628 on the patient and their caregiver(s), and the efficacy, safety, and accessibility of the
629 interventions. While some systemic AD clinical trials do not allow for the use of topical

therapies, in clinical practice it is common to employ topical treatments concomitantly with systemic agents.

Monoclonal antibodies

Over the last five years, monoclonal antibodies (biologics) have changed the landscape of pediatric AD treatment. They are effective in severe cases, refractory to optimized topical therapies, and are safe with few side effects. Dupilumab, which blocks the IL-4 receptor alpha subunit and inhibits signaling from IL-4 and IL-13, was the first to gain approval, followed by tralokinumab and lebrikizumab, both IL-13 blockers, and nemolizumab an IL-31 blocker. Omalizumab, an IgE antibody, was also studied in pediatric AD patients with mixed results, and does not have FDA approval for AD.[153]

Dupilumab

The work group recommends dupilumab for children 6 months and older with moderate-to-severe AD (**Table V**). There are less efficacy and safety data on children aged 6 months to under 2 years than for older age groups. Shared decision-making with caregivers and adequate use of topicals is particularly important for all systemic therapies in this very young population. Dosing is tiered by weight and age, but consideration should be given to spacing the doses to every four weeks during childhood given the trauma of injection (**Table VI)**. Moreover, efficacy data were relatively equivalent comparing 300 mg every 4 weeks and 200 mg every 2 weeks in children 30-60 kg; the European Medicines Agency recommends dosing for this group at 300 mg every four weeks rather than the FDA-recommended 200 mg every 2 weeks.

In adolescents (12-18 years of age) with AD, dupilumab resulted in significantly more patients with IGA 0 or 1 and a clinically meaningful reduction in the SCORAD at 16 weeks (while placebo did not) (**Supplemental Table 28**).[99] Furthermore, dupilumab resulted in significant itch improvement, POEM reduction, fewer flares, and improved QoL. Serious treatment-emergent AEs do not appear to be greater with dupilumab than placebo and withdrawals due to AEs were rare and similar across treatment arms. Conjunctivitis, a well-known potential AE of dupilumab, occurred in 9.8% of dupilumab patients vs. 4.7% of placebo patients. Similar findings were described in patients 6-11 years of age with severe AD inadequately controlled with topical therapies; in this RCT, both groups were allowed to use topical steroids as needed (**Supplemental Table 29**).[97] Data for children aged 6 months to 6 years with moderate-to-severe AD was also similar to the data for adolescents in terms of IGA 0 or 1 achievement (RR 7.30 [95% CI 2.28 to 23.35]), QoL improvement, and SCORAD, itch, POEM, and flare reduction (**Supplemental Table 30**).[98] More importantly, in this vulnerable age group, treatment-related severe/serious AEs and withdrawals due to AEs were equivalent to standard care. Uncontrolled extension data in adolescents over 52 weeks continues to demonstrate effectiveness and safety.[96]

Tralokinumab

An RCT of 182 adolescent AD patients with TCS/TCI treatment failure demonstrated significant improvement compared to placebo in EASI, IGA, and SCORAD with tralokinumab (**Supplemental Table 31**). Patients in the treatment group had better QoL outcomes and fewer SAEs.[100] There were no withdrawals in either arm. Extension data to 52 weeks continued to demonstrate effectiveness (EASI 75: 37/70 [52.9%]) and safety.

Lebrikizumab

In two RCTs that included 102 adolescents (aged 12 to 18 years) with moderate-to-severe AD, lebrikizumab had positive effects on IGA 0 or 1, EASI 75, and pruritus improvement.[101] Non-randomized cohort data demonstrated a clinically meaningful improvement in QoL, long-term safety and tolerability, and robust long-term (52-week) efficacy (**Supplemental Table 32**).[102] Combined with topical steroids, lebrikizumab may result in even higher proportions of IGA 0 or 1 and EASI 75 responses, with similar pruritus improvement;[101] but limited QoL difference compared to TCS alone (**Supplemental Table 33**).[103]

Nemolizumab

Two trials, including 266 adolescents (12 years and over) with moderate-to-severe AD, evaluated the efficacy and safety of nemolizumab every four weeks compared to placebo, both administered with TCS and with or without TCIs. Nemolizumab and concomitant topical therapy significantly increased the number of adolescents achieving meaningful itch reduction, EASI75, and IGA success, with little to no difference in rates of serious AEs or discontinuation (**Supplemental Table 34**).[104] A small trial of 89 children aged 6 to 12 years compared nemolizumab every four weeks to placebo, both in combination with TCS, TCIs, or systemic antihistamines. In this trial nemolizumab resulted in a significant increase in the number of children achieving meaningful itch improvement, IGA success, and at least a 2.5 point improvement in CDLQI, with little to no difference in the number of serious AEs or discontinuation (**Supplemental Table 35**).[105]

Omalizumab

FDA-approved for chronic idiopathic urticaria in patients 12 years and older, omalizumab does not have FDA approval for AD treatment. The workgroup did not give a recommendation for this treatment due to insufficient evidence (**Supplemental Table 36**). In a trial of 60 adolescent (12-19 year old) AD patients, omalizumab resulted in a clinically meaningful reduction in EASI, but the impact on other outcome measures (e.g. POEM score, flares, Children's Dermatology Life Quality Index [CDLQI]) was less clear but probably favorable.[153] Rates of AEs and withdrawal were equitable across treatment arms. While the single RCT suggests benefit, there are well-known risks of therapy that need to be considered, particularly allergic reactions to the medication early in the course. Additionally, the totality of available evidence on the use of omalizumab for AD suggests no clear benefit.[154,155]

JAK inhibitors

JAK inhibitors are another systemic option for AD. Effective in other disciplines, including oncology and rheumatology, they are used to treat severe alopecia areata, psoriasis, AD, and other skin conditions. As mentioned previously with topical ruxolitinib, JAKis carry several black box safety warnings. While evidence to date is reassuring for their safety in otherwise healthy dermatology patients, including children, caution is recommended when using these medications, including appropriate laboratory monitoring.

Of the systemic JAKis, upadacitinib and abrocitinib have FDA approval for AD in patients as young as 12 years of age who have failed other systemic therapies or when use of those therapies is inadvisable. "Failure" as it appears in the recommendation is not simply an inadequate therapeutic response but also encapsulates intolerable side effects, among other considerations.

Systemic JAKis come in oral form, which needle-phobic patients may prefer to monoclonal antibody treatments, even though laboratory testing is required for JAKis.

Abrocitinib

In a RCT including 50 adolescents with moderate-to-severe AD, 43.8% receiving abrocitinib vs 0% receiving placebo achieved EASI 75, and 12.5% receiving abrocitinib vs. 0% receiving placebo achieved IGA 0 or 1 response and a ≥ 2 grade improvement from baseline (**Supplemental Table 37**).[114] In two other RCTs, abrocitinib resulted in an improvement in POEM, itch, and QoL.[111] Combining abrocitinib with prescription topical treatments results in similarly positive outcomes and a favorable safety profile (**Supplemental Table 38**).[115] A safety analysis including adults and adolescents found people who were given abrocitinib were more likely to report nausea, headache, and acne than people given placebo. These AEs were typically mild or moderate and did not result in discontinuation of treatment.[113] Herpes simplex infection was more common in people taking abrocitinib (4/100 participants for 200 mg and about 3 /100 participants for 100 mg) than in people who took placebo (2/100 participants); herpes zoster may also occur more frequently in those on abrocitinib.

Baricitinib

Baricitinib is not FDA-approved for use in AD, but it is approved for AD in children ≥2 years old in Europe and the work group recommends its use based on moderate certainty evidence (**Supplemental Tables 39-40**). In the primary RCT of 242 moderate-to-severe AD patients aged 2 -17 years, both the 2 mg daily and 4 mg daily dosing schedules were effective, but the 4 mg

dose resulted in a higher proportion of patients achieving vIGA-AD 0-1 and meaningful reductions in EASI score.[116] With both doses, serious AEs and withdrawal due to AEs were low.

Upadacitinib

Like the previously mentioned systemic JAKis, upadacitinib was also shown to be effective in adolescents with AD (**Supplemental Tables 41-42**). In 2 RCTs including 177 adolescent patients, percent reduction in EASI from baseline was -23.9 with placebo vs -77.3 with upadacitinib.[106] Furthermore, significantly more patients had meaningful itch reduction (numeric rating scale score $\geq$ 4) and CDLQI reduction. Another RCT of adolescent AD patients comparing upadacitinib in combination with TCS compared to placebo with TCS described similar findings.[110] Serious AEs and withdrawal due to AEs were low. The most common treatment-emergent AEs were acne (11.5% vs 2.5%), headache (6.6% vs 3.3%), upper respiratory tract infections (9% vs 5%), creatine phosphokinase level elevations (6.6% vs 2.5%) and nasopharyngitis (4.1% vs 2.5%).[107] However, treatment-emergent AEs of interest were infrequent with no significant difference between groups in terms of serious infection; no opportunistic infections, active tuberculosis, malignant neoplasms (including nonmelanoma skin cancer), or any adjudicated major adverse cardiac events, venous thromboembolisms, or events of gastrointestinal perforation were reported in adolescents. This favorable AE profile was also described in another RCT studying upadacitinib in combination with TCS.[108] Extension data at 112 weeks demonstrated sustained efficacy and found no new safety signals, though absolute numbers were small (19 patients).[109] Of note, the FDA approved a starting dose of 15 mg daily, but stated that the dose can be increased to 30 mg daily if there is an inadequate response; based on the available data, we feel that 4-12 weeks is an appropriate time to assess response.

Antimetabolites

Methotrexate

Though it does not have FDA approval, before the emergence of monoclonal antibodies and JAKis, methotrexate was used more commonly to control moderate-to-severe AD. It is still an effective option, but comorbidities or drug interactions that may exacerbate toxicity render it inappropriate for select patients.

In a small RCT of children aged 8-14 years with severe AD comparing methotrexate 7.5 mg weekly (initial dose of 5 mg) to cyclosporine 2.5 mg/kg/day for 12 weeks, both treatments resulted in meaningful SCORAD reductions (**Supplemental Table 43**).[156] However, methotrexate showed a later relapse than cyclosporine (20 weeks vs 14 weeks on average). Both medications appeared to be safe with no withdrawals. In a similar RCT comparing high-dose cyclosporine (up to 5 mg/kg/day) to methotrexate (0.4 mg/kg weekly – maximum dose of 25 mg weekly) for 36 weeks, high-dose cyclosporine resulted in a higher proportion of patients achieving EASI-50 at 12 weeks but a lower proportion by 36 weeks (**Supplemental Table 44**).[117] Both treatments were similar in terms of POEM scores, flares (though methotrexate performed better), and CDLQI. Serious AEs and withdrawal due to AEs were similar between groups. Given the well-known risks of methotrexate, it is advisable to conduct conservative laboratory monitoring, particularly to look for hepatic and hematologic AEs.

Immunosuppressants

Systemic corticosteroids

The workgroup's good practice statement against systemic corticosteroids as a long term treatment for AD is based on a body of indirect evidence on the harms of systemic steroids in other inflammatory skin diseases and adults (**Supplemental Table 45**).[157] Efficacy data were very low certainty (i.e. no direct RCTs), but the certainty of the harms data is higher. The harms are of particular concern in the pediatric population due to their significant impact on growth and bone formation.

Schmitt et al. compared prednisolone (0.5-0.8 mg/kg tapered to 0 over 2 weeks) to cyclosporine (2.7-4.0 mg/kg/day for 6 weeks) in adults with severe AD.[127] Both treatments resulted in clinically meaningful reductions in SCORAD at 6 weeks, but the trial stopped early due to safety issues based on the high rate of relapse in the prednisolone group; as a result, treatment discontinuation was common in both arms but higher with prednisolone due to the high rate of relapse.

The use of systemic steroids should be reserved exclusively for acute, severe exacerbations as a short-term bridge therapy to other steroid-sparing treatments. Systemic steroids have no role in long-term maintenance treatment for AD, particularly in children.

Mycophenolate mofetil

There was no direct evidence for the use of mycophenolate mofetil (MMF) in the management of children or adolescents with AD (**Supplemental Table 46**). A conditional recommendation with

proper monitoring was given despite a lack of FDA approval and scant data, as MMF can be a safe and effective treatment in certain severe AD cases (**Table V**). Nonetheless, comorbidities or drug interactions that may exacerbate toxicity make this intervention inappropriate for select patients.

A non-inferiority trial in adults with severe AD comparing enteric-coated mycophenolate sodium 1440 mg/day to cyclosporine A 3 mg/kg/day as maintenance therapy after a 6-week run-in phase of cyclosporine A 5 mg/kg/day found at 10 and 33 weeks, SCORAD scores remained comparable with no SAEs reported in either arm.[119] The authors concluded mycophenolate sodium was as effective as cyclosporine A for maintenance therapy. A systematic review and meta-analysis of individual patient data reported that for patients with refractory AD (mean age 38.21±22.8) there was a statistically significant reduction in SCORAD scores following MMF treatment: Mean difference (MD) 18.01 (95% CI 8.54, 27.48, p = 0.0002; n = 37).[120] Across the 140 patients included in the review, MMF was effective (complete or partial remission) in 77% with relapses occurring in 8.2%. The most common AEs reported were headaches (10.7%), gastric discomfort (10.7%), herpes infection (9.3%), deranged liver function tests (7.9%), and other infections (6.4%).

Azathioprine

As with MMF, the workgroup gave a conditional recommendation for azathioprine but only for limited-term use and with proper monitoring and prescreening of thiopurine methyltransferase activity to ensure safety (**Table VI**). The evidence is sparse and of high risk of bias due to limited methods reporting and selective outcome reporting (**Supplemental Table 47**).[122] Furthermore,

834 the study sample (adolescents and adults aged 16 years and over) differs from the population of
835 interest, but the data suggest an improvement in Six Area, Six Sign Atopic Dermatitis Severity
836 score, itch, and Dermatology Life Quality Index.
837
838 *Cyclosporine*
839 While it is not FDA approved for use in pediatric AD, cyclosporine is approved by the European
840 Medicines Agency for severe AD in individuals 1 year of age and older. We recommend it
841 conditionally for limited-term use with proper monitoring (**Table V**).
842
843 Cyclosporine was already discussed above in trials comparing it to methotrexate. No direct
844 evidence was identified to assess the management of AD in children or adolescents with
845 cyclosporine (**Supplemental Table 48**). In adults, cyclosporine was shown to be superior to
846 phototherapy,[124] oral prednisolone[127] and similar to methotrexate[123] and extracorporeal
847 photopheresis.[125]
848

Systemics with insufficient evidence

The following systemic agents had insufficient evidence to make a recommendation regarding the treatment of pediatric AD: intravenous immunoglobulin, interferon gamma, systemic calcineurin inhibitors (other than cyclosporine), systemic antibiotics, oral antihistamines, and systemic antivirals for eczema herpeticum (**Supplemental Tables 49-51**). However, if recommended options are ineffective, they could be considered. See **Supplemental Appendix 2** for assessments of the evidence related to each of the interventions above.

Cost

Assessing the certainty of the best available evidence for net therapeutic benefit and consideration of patient values and preferences are the primary drivers of recommendation development in AAD guidelines. However, the workgroup recognizes that costs for some recommended therapies may be prohibitive without adequate insurance coverage. Cost should be considered during the shared decision-making process.

Gaps in Research

While there is no shortage of studies describing the efficacy of moisturization in AD, we still do not know the optimal ingredients and formulations. A recent study comparing four different types of emollients in children with AD found no difference in effectiveness between the groups, which may indicate (for now) that using any type of moisturizer may be helpful.[158] Furthermore, there are unanswered questions when it comes to wet dressings (and how to optimally utilize them), as well as bathing.

From a therapeutic standpoint, there are more treatments for patients with AD than ever before. At the time of this publication, for example, there are 5 non-steroidal topical agents for AD. However, many of these new medications are costly and access can be challenging. More head-to-head studies comparing new medications to older generic TCS in terms of efficacy and safety are needed. Furthermore, more pediatric-specific data, particularly for older agents, will also be helpful for providers when they are making therapeutic decisions for their patients. With a variety of biologics and oral JAKis available, it is easy to overlook cheaper yet effective immunosuppressive agents and NB-UVB phototherapy. It would be useful to have studies examining these agents and how they compare with newer agents in the pediatric population. Many studies of older agents are specific to adults or at least not exclusive to children, making recommendations specific to children more challenging.

Conclusions

We provide 19 evidence-based recommendations on the medical management of AD in pediatric patients We make strong recommendations for the use of moisturizers, topical calcineurin inhibitors, topical corticosteroids, crisaborole ointment, roflumilast cream, ruxolitinib cream, tapinarof cream, dupilumab, tralokinumab, lebrikizumab, upadacitinib, abrocitinib, and baricitinib in the treatment of pediatric AD. Conditional recommendations were made in favor of bathing, bleach baths, wet dressings, phototherapy, methotrexate, mycophenolate mofetil, azathioprine, and cyclosporine. We conditionally recommend against the use of topical antimicrobials, PUVA phototherapy, and strongly recommend against long term use of systemic corticosteroids.

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