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Practice Parameters

Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE– and Institute of Medicine–based recommendations

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Refer to the eAppendix for additional details and practical considerations.

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ABSTRACT

Background: Guidance addressing atopic dermatitis (AD) management, last issued in 2012 by the American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force, requires updating as a result of new treatments and improved guideline and evidence synthesis methodology.
Objective: To produce evidence-based guidelines that support patients, clinicians, and other decision-makers in the optimal treatment of AD.
Methods: A multidisciplinary guideline panel consisting of patients and caregivers, AD experts (dermatology and allergy/immunology), primary care practitioners (family medicine, pediatrics, internal medicine), and allied health professionals (psychology, pharmacy, nursing) convened, prioritized equity, diversity, and inclusiveness, and implemented management strategies to minimize influence of conflicts of interest. The Evidence in Allergy Group supported guideline development by performing systematic evidence reviews, facilitating guideline processes, and holding focus groups with patient and family partners. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach informed rating the certainty of evidence and strength of recommendations. Evidence-to-decision frameworks, subjected to public comment, translated evidence to recommendations using trustworthy guideline principles.
Results: The panel agreed on 25 recommendations to gain and maintain control of AD for patients with mild, moderate, and severe AD. The eAppendix provides practical information and implementation considerations in 1-2 page patient-friendly handouts.
Conclusion: These evidence-based recommendations address optimal use of (1) topical treatments (barrier moisturization devices, corticosteroids, calcineurin inhibitors, PDE4 inhibitors [crisaborole], topical JAK inhibitors, occlusive [wet wrap] therapy, adjunctive antimicrobials, application frequency, maintenance therapy), (2) dilute bleach baths, (3) dietary avoidance/elimination, (4) allergen immunotherapy, and (5) systemic treatments (biologics/monoclonal antibodies, small molecule immunosuppressants [cyclosporine, methotrexate, azathioprine, mycophenolate, JAK inhibitors], and systemic corticosteroids) and UV phototherapy (light therapy).

Executive Summary—American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Atopic Dermatitis Guidelines

Aims of These Guidelines and Specific Objectives

The purpose of these guidelines is to provide evidence-based recommendations about optimal management of atopic dermatitis (AD; [atopic] eczema) in infants, children, and adults. The guidelines address the following 5 main management questions:

1. Among patients with AD, what topical treatments should be used to achieve optimal outcomes?
2. Should elimination diets (dietary avoidance strategies) be used for AD?
3. Should dilute bleach baths be used for AD?
4. Should allergen immunotherapy be used for AD?
5. Among patients with AD, what systemic treatments, including phototherapy (UV light therapy), should be used to achieve optimal outcomes?

The target audience includes patients, AD specialists (allergists/immunologists and dermatologists), family medicine physicians, pediatricians, and other decision-makers. This document may also serve as the basis for adoption or adaptation by local, regional, or national guideline panels and policymakers.

What Is New and Different

These Joint Task Force on Practice Parameters (JTFPP) guidelines represent an evolution in trustworthy allergy guidelines[1] and are distinguished from other guidelines[2,3] through systematic reviews of the evidence with multidisciplinary panelist engagement, adherence to rigorous guideline development processes, robust use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) that fulfills requirements to report its proper use,[4] the core involvement of the patient and caregiver voice from start to finish, focus on equity, diversity, and inclusiveness (including concepts addressing AD in diverse skin tones [skin of color] and health disparities), clear translation of evidence to clinically actionable and contextual recommendations, and novel approaches to facilitate knowledge translation.[5,6] The guidelines emphasize, in addition to standards of trustworthiness, the third principle of evidence-based medicine: that evidence alone is never

enough; that patient values and preferences must be carefully considered when determining optimal treatments for patients and populations.[7,8] The eAppendix provides 1-2 page patient-friendly handouts to facilitate education, discussion, and shared decision-making.

The current guidelines also differ from our previous guidelines in a few other ways. The 2012 Atopic Dermatitis Practice Parameter[9-11] covered a wide range of topics such as immunopathology, diagnosis, and trigger factors and was a revision of the 2004[12] and 1997 guidelines[13]; the 2023 guidelines focused on 5 main questions addressing therapy. In the last 10 years, multiple new therapies have emerged, including multiple biologics, small molecules, and a topical PDE4 inhibitor. These are well covered in the 2023 guidelines.

Some of the important changes in this updated practice parameter include the following (Fig. 1):

- Guidance on shared decision-making and factors to consider for each recommendation
- Recommends the use of topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs) in patients with uncontrolled AD despite moisturizer use
- Highlights the safety of TCIs with typical use once or twice daily
- Consideration for once-daily dosing of topical medications
- Suggests using crisaborole 2% ointment for mild-to-moderate AD
- Suggests against adding topical JAK inhibitors, such as ruxolitinib, for patients with mild-to-moderate AD refractory to moisturization alone
- Suggests against the use of topical antimicrobials for AD alone with no infection
- Recommends proactive therapy with TCS or TCI for patients with a relapsing course
- Suggests bleach baths for patients with AD with moderate-to-severe disease as an additive therapy; suggests against bleach baths for those with mild AD
- Suggests against elimination diets for AD
- Suggests allergen immunotherapy (AIT) for moderate-to-severe AD
- Recommends dupilumab for patients 6 months of age or older or tralokinumab for patients aged 12 years and older, with moderate-to-severe AD refractory, intolerant, or unable to use midpotency topical treatment
- Suggests use of oral JAK inhibitors after careful consideration of risks and possible benefits in adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously
- Recommends against using baricitinib 1 mg, and suggests against azathioprine, methotrexate, and mycophenolate mofetil
- Suggests consideration of cyclosporine in adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and biologics
- Suggests against the use of systemic corticosteroids for AD
- The eAppendix supplement provides 1-2 page patient-friendly handouts to facilitate education, discussion, practical considerations, and shared decision-making
- Commitment to update and revise the recommendations as part of living guidelines

Executive Summary of Recommendations

This update is focused on 5 important questions for the management of AD. Answering these 5 questions provides an excellent framework for managing AD. The infographic (Fig 1) summarizes the recommendations in a format that is easily scalable and shareable, in its unmodified entirety, through social media, flyers, print (eg, 2 pages side by side or a single double-sided page), and as posters (eg, posted in clinician offices). To start, the guidelines provide a Good Practice Statement for care of AD.

Good Practice Statement

Clinicians managing all severities of AD should, before issuing any new therapy, perform the following:

(1) ensure the correct diagnosis and identify complicating diagnoses
(2) provide education, for instance an information guide about the disease and an action plan
(3) address trigger avoidance
(4) ensure proper medication use and adherence
(5) encourage application of a bland moisturizer titrated to symptomatic benefit (at least once, often multiple times, per day)

Systematic reviews and a recent large randomized trial suggest that the best moisturizer is the one that patients will use regularly, and shared decision-making should express the potential tradeoffs between benefits (eg, perhaps greater benefit with ointment-based moisturizers for more severe disease) and acceptability.

Topical Therapies

Moisturizers are critical for AD care, and several prescription moisturizers have become available in the last several years. On the basis of available evidence, the panel suggested against the use of prescription moisturizers (formally marketed as prescription medical devices).[14] Given the close balance vs possible alternatives (over-the-counter moisturizers), the panel inferred that most well-informed patients would place a higher value on avoiding the burdens, inconvenience, and cost that are more likely to be the case with prescription moisturizers.

Topical corticosteroids (also called topical steroids) are the mainstay of therapy for AD. In patients with uncontrolled AD refractory to moisturization alone, the JTF panel recommends addition of a TCS with high-certainty evidence.[14] The TCS, used in randomized clinical trials (RCTs) mostly for 2 to 6 weeks, probably did not importantly increase adverse effects, including skin infections, atrophy, or other local skin changes. Exactly which TCS to use depends on a patient's previous treatment history, site of application, cost, accessibility, and values and preferences. Avoid high-potency (classes 1 and 2; examples of each potency are provided in the guideline tables) TCS for prolonged continuous periods of time (>4 weeks), and limit its use on sensitive areas (face, folds, groin)—rare instances of atrophy, telangiectasia, and striae may be more likely to occur in these cases. Continuous and prolonged use of lower potency TCS on sensitive areas can also cause these effects. The guideline text and eAppendix detail monitoring response to therapy and provide considerations for difficult-to-control AD. Prescribing more than one potency of topical treatment to be used at different sites of the body, or depending on the severity of AD activity, must be balanced against the potential for polypharmacy, which can increase confusion, cost, and patient and family burden, albeit these barriers might be mitigated with clear action plans. After addressing active disease ("gaining control" or "inducing remission"), TCSs are also strongly recommended for continued intermittent therapy to prevent future flares ("keeping control" or "proactive therapy").[14]

Topical calcineurin inhibitors are important topical therapies for AD. In patients aged 3 months or older with uncontrolled AD refractory to moisturization alone, the JTF panel recommends addition of a TCI (pimecrolimus or tacrolimus) with high-certainty evidence.[14] Pimecrolimus efficacy across multiple AD outcomes is intermediate between TCS 5 and TCS 6/7. Tacrolimus 0.03% is similar to TCS 5. Tacrolimus 0.1% is similar to TCS 4. Topical calcineurin inhibitors may also be used as continued intermittent or proactive therapy. Select review of studies of animals exposed to supraphysiological doses of systemic calcineurin inhibitors, extrapolation from systemic use among patients after organ transplant, and data from uncontrolled voluntary reporting systems led the Food and Drug Administration (FDA) to add a boxed warning to TCIs in 2006 and 2011 associating them with cancer. In contrast, a linked systematic review of all randomized and observational evidence (more than 3.4 million patients

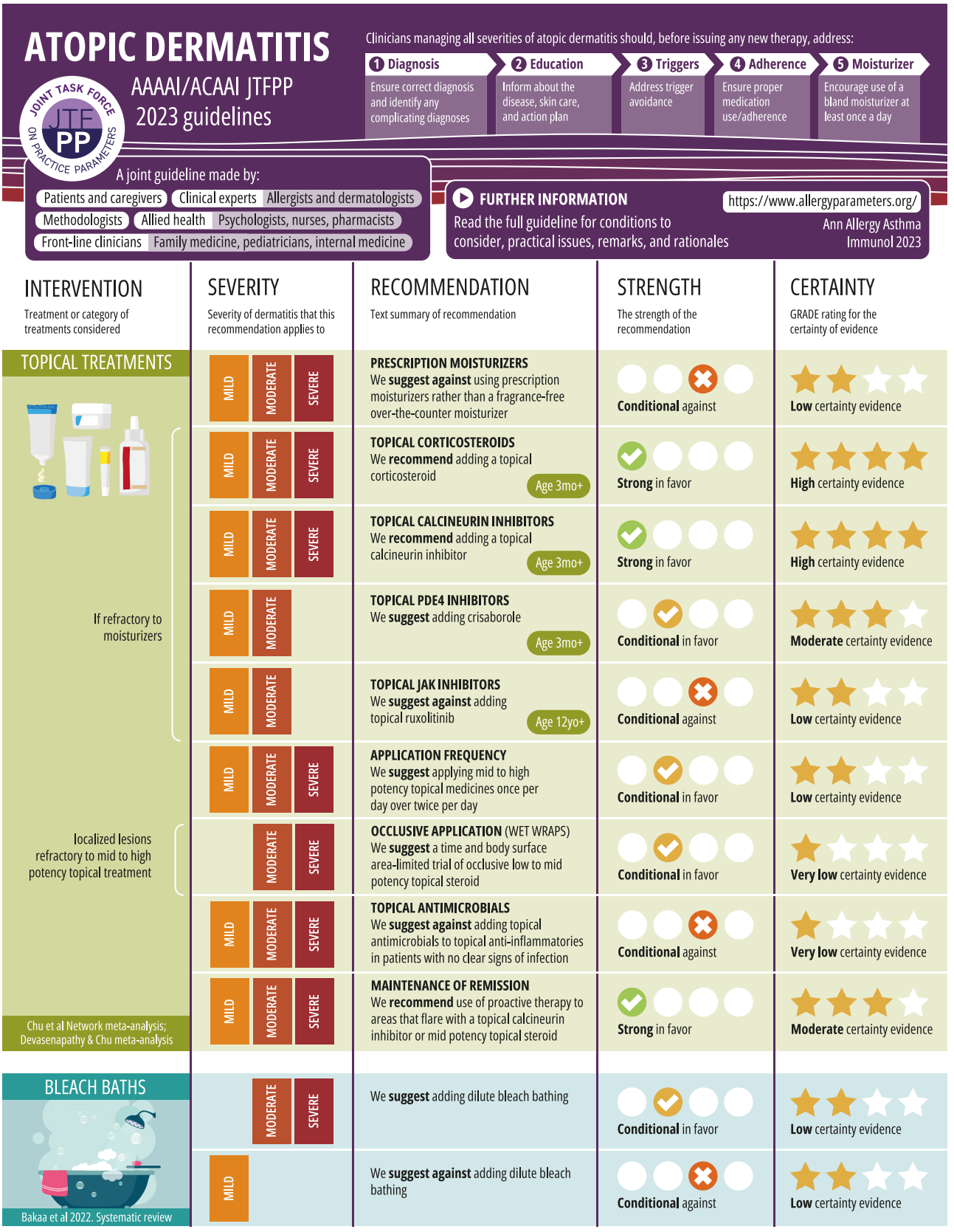

Figure 1. Recommendations infographic. AAAAI, American Academy of Allergy, Asthma and Immunology; ACAAI, American College of Allergy, Asthma and Immunology; JTFPP, Joint Task Force on Practice Parameters.

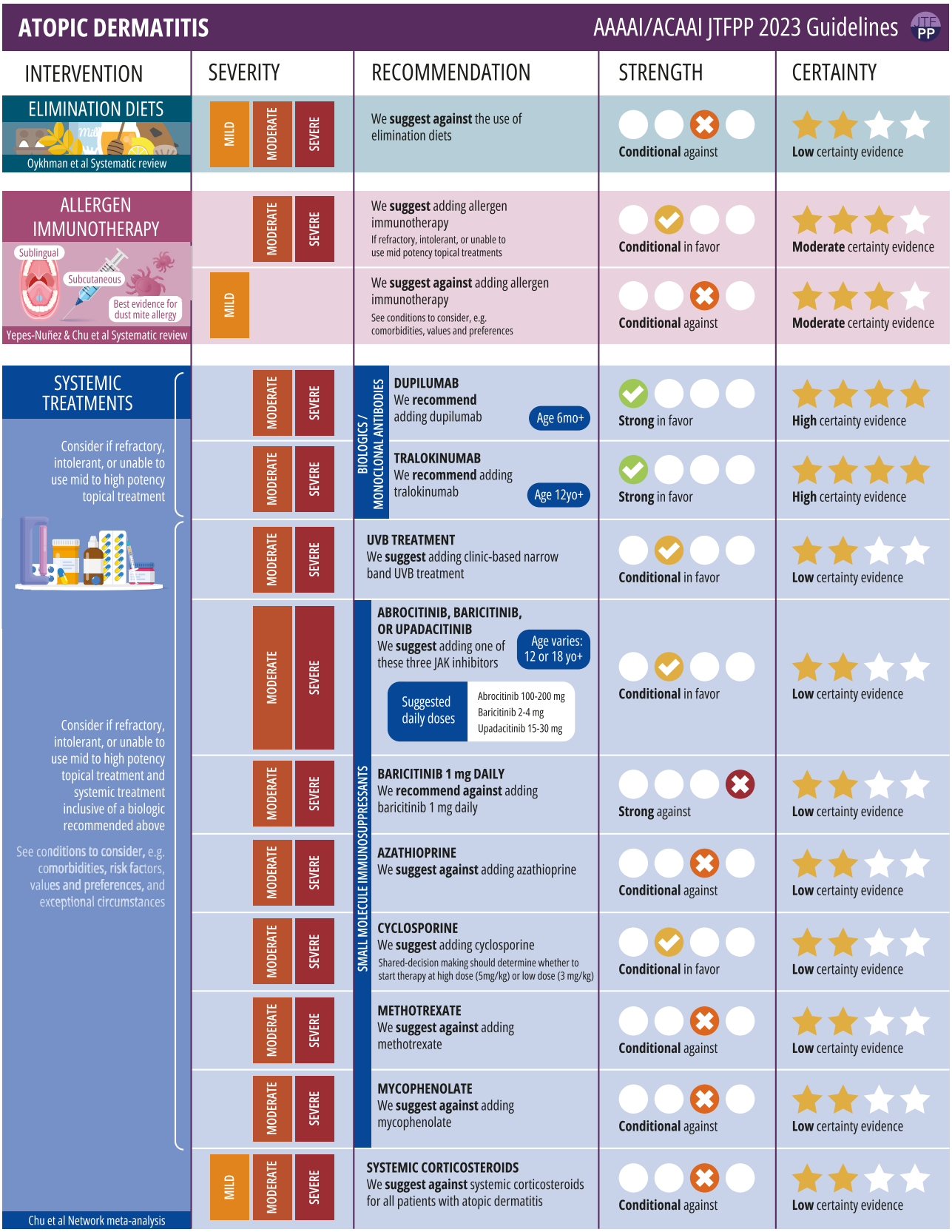

Figure 1 Continued.

followed for up to 10 years), and incorporating patient values and preferences, revealed no credible increase in cancer with a broad range of typical TCI use among infants, children, and adults (4.56 per 1000 incidence across all ages without TCIs vs 4.70 per 1000 with TCIs).[15] Minor harms of TCIs include local irritation/burning.

The JTF panel also addressed once-daily vs 2 or more times per day application of TCSs or TCIs and suggests applying the medication once per day rather than twice per day.[14] Patients who value a simpler treatment routine, potentially lower chance for adverse effects, and using less overall medication may prefer once per day application over twice per day application. Patients with a more severe flare or who might value resolving it more quickly may prefer twice per day application over once per day application.

Bleach Baths

There has been controversy over whether dilute bleach baths may help AD. The linked systematic review and meta-analysis synthesizing 10 RCTs[16] revealed that the probability to improve AD severity by 50% with adjunctive dilute bleach baths was 32% vs 22% in the control group (moderate certainty). There was little to no difference in adverse events, with mild events consisting of dry skin and irritation noted. Changes in other patient-important outcomes (eg, itch, patient-reported disease severity, sleep quality, AD-related quality of life, and risk of AD flares) were uncertain. Given this relatively minor improvement, the panel suggests that dilute bleach baths may be beneficial in patients with moderate and severe AD. Written instructions will be needed to ensure that patients use the correct type and concentration of bleach (see eAppendix for examples and practical information as a 1-page double-sided handout). Some patients may not have access to a bathtub and may find bleach baths too much effort. In patients with mild disease, the limited magnitude of improvement was not felt to justify the burden.

Elimination Diets

Patients with AD have a higher risk for food allergies than those without AD. Food allergy testing and elimination diets are often considered to try to inform how to improve AD control. Recent evidence, however, suggests that tolerance to food allergens is promoted through frequent, and perhaps high-dose, oral exposure. Avoidance of food allergens is therefore strongly associated with promoting the development of IgE-mediated food allergy. The linked systematic review and meta-analysis identified 10 RCTs (599 participants) addressing benefits and harms of dietary elimination for AD.[17] Compared with no dietary elimination, low-certainty evidence revealed that dietary elimination may slightly improve AD severity (50% with vs 41% without dietary elimination improved by a minimally important difference, risk difference [RD] of 9% [95% CI, 0-17]), pruritus (daytime itch score [range, 0-3] mean difference [MD], −0.21 [95% CI, −0.57 to 0.15]), and sleeplessness (sleeplessness score [range, 0-3] MD, −0.47 [95% CI, −0.80 to −0.13]). Bayesian sensitivity analyses revealed that most individuals pursuing a diet elimination strategy would most likely experience little to no benefit. The JTF panel suggests against the use of elimination diets compared with an unrestricted diet. Between both the uncertain benefits and uncertain harms,[17] including the potential risk of promoting food allergy, the panel inferred that most well-informed patients would place a higher value on avoiding potentially large harms. This was particularly the case in infants and children whom the risk for developing food allergy is thought to be greater. All ages, however, were thought to be at risk of malnutrition and burdensome to patients and their caregivers with following a strict dietary elimination strategy.

Allergen Immunotherapy

The previous practice parameter noted that AIT could be effective for AD. This guideline's linked systematic review of 23 RCTs (11 subcutaneous immunotherapy [SCIT] and 12 sublingual immunotherapy [SLIT]) included 1957 adult and pediatric patients (median of study mean ages, 19 years; range of means, 4-34 years).[18] Most studies desensitized patients to house dust mites (HDMs; *Dermatophagoides pteronyssinus* and/or *D farinae*), whereas 4 included other inhaled allergens (eg, pollens). Patients were mostly on standard topical therapy including TCSs and moisturizers with AIT added on. Furthermore, most studies included polysensitized patients in addition to HDM sensitization. Based on a combination of clinician-reported AD severity (eg, SCORing Atopic Dermatitis [SCORAD]), AIT likely improved AD severity by 50% or more from baseline compared with no AIT (40% vs 26%), with similar estimates of effect for SCIT and SLIT. The main adverse effects were similar to AIT for allergic rhinitis and asthma, that is, local injection site reaction for SCIT (66% of individuals) and oropharyngeal itching for SLIT (13% of individuals). Systemic reactions or those severe enough to cause discontinuation occurred in approximately 10% of those receiving SCIT and were rare with SLIT (0.14% systemic reaction; 1.2% discontinue). The panel inferred that most well-informed patients would value the moderate certainty for net benefit with AIT for moderate and severe AD especially if the patient had other allergic diseases that would respond to AIT. The panel noted that there would be variability in patient values and preferences regarding the burden associated with SCIT (multiple clinician visits for administration; often starting as weekly) and SLIT (daily self-administered medication) and time to effect.

Systemic Treatments Including Ultraviolet Phototherapy (Light Therapy)

There are multiple approved options for systemic treatment of AD refractory to, at least, topical therapy. Such patients will often have moderate-severe disease. These therapies include biologics, small molecules (mostly immunosuppressants), and UV light therapy (phototherapy).[19]

The currently approved biologics target IL-4 and IL-13 cytokine signaling pathways, or IL-13 signaling alone. Dupilumab binds a common receptor IL-4Rα and inhibits IL-4R signaling induced by both IL-4 and IL-13. Tralokinumab binds to the IL-13 cytokine in an epitope that overlaps with the binding site of the IL-13Rα receptors, preventing IL-13 from binding to the receptor. The linked systematic review and network meta-analysis (NMA) revealed that, compared with continued standard topical treatment alone, adding dupilumab or tralokinumab led to improvements in multiple patient-important outcomes. The improved outcomes included AD signs and symptoms, judged either by patients or clinicians, itch, and sleep disturbance. There was no clear increase in serious adverse events or adverse events leading to discontinuation.[19] Conjunctivitis, however, was higher with dupilumab or tralokinumab in comparison to placebo.[19] The linked systematic review of patient values and preferences for treatment of AD,[20] along with direct patient and caregiver input, revealed that patients with AD value stepping-up therapy based on severity, safe medications, relief and normalization of daily activities, and a strong patient-provider relationship, despite the need for injections and potential fear of needles. Compared with dupilumab, tralokinumab was one category lower in efficacy across multiple patient-important outcomes.[19] Tralokinumab is approved for AD in ages 12 years and older. Dupilumab is approved for children/adults aged 6 months and older for AD and asthma (ages 6 years and older), eosinophilic esophagitis (ages 12 years and older), and, for adults, chronic rhinosinusitis with nasal polyposis and prurigo nodularis. Patients and caregivers may also value having one systemic therapy treat multiple conditions.

There are multiple oral JAK inhibitors currently available and additional ones in development. The linked systematic review and NMA revealed that the benefits and harms of JAK inhibitors (in alphabetical order), abrocitinib, baricitinib, and upadacitinib, varied by drug and increased with dose of each medication.[19] Although mild and common harms (eg, acne, minor infection) increased with the dose of each medication, data addressing less common serious harms were hampered by the short duration of studies (16 weeks typically).[19] For example, although serious infections such as herpetic

infections (eg, eczema herpeticum, herpes zoster) were consistently increased in patients with AD using all 3 studied oral JAK inhibitors, there were no clear increase in deaths, cancer, or thrombosis detected in the short studies done.[19] The FDA placed a Boxed Warning label on the oral JAK inhibitors due to a recent study in rheumatoid arthritis using tofacitinib.

The risk-benefit profile of JAK inhibitors should be considered when selecting JAK inhibitors in clinical practice. Risk considerations should include both observed safety data for the individual drugs from clinical trials of patients with AD and class-wide theoretical safety concerns and boxed warnings for JAK inhibitors from the US FDA. Oral JAK inhibitors are contraindicated in pregnancy and breastfeeding. Risk factors for adverse outcomes, including age or other strong risk factors for cancer, serious infection, venous thrombosis, or cardiovascular disease, favor against JAK inhibitor use in these populations. JAK inhibitors are immunosuppressants and therefore screening for conditions before use (eg, age-appropriate cancer screening, active or latent tuberculosis or viral hepatitis, vaccination including herpes zoster, cytopenias, diverticular disease or bowel perforation, renal and liver function, pregnancy) and subsequent clinician and patient monitoring for adverse effects are required. These can range in severity from acne, abdominal pain, easy bruising, tiredness, and blood abnormalities (lipids and other biochemistries, cell counts) to the serious harms described previously. There are thus multiple implementation considerations, detailed in the eAppendix, including drug-drug interactions, laboratory and clinical monitoring, FDA-approved doses, and practical considerations.

The American Academy of Allergy, Asthma and Immunology/ American College of Allergy, Asthma and Immunology Joint Task Force Guidelines for Management of Atopic Dermatitis

Aims of These Guidelines and Specific Objectives

The purpose of these guidelines is to provide evidence-based recommendations about optimal management of AD ([atopic] eczema) in infants, children, and adults.

The target audience includes patients, AD specialists (allergists/immunologists and dermatologists), family medicine physicians, pediatricians, and other decision-makers. This document may also serve as the basis for adoption or adaptation by local, regional, or national guideline panels and policymakers.

Scope of Atopic Dermatitis

AD spans nations, age groups, ethnicities, and cultures.[21] To provide context to the guideline recommendations, we briefly review the scope of the health problem, pathophysiological mechanisms, and populations, before describing the guideline methods and recommendations.

The Health Problem and Burden of Disease

AD is the most common chronic inflammatory skin disease, and studies in the past 20 years reveal that it affects approximately 13% of children and 7% of adults[22-25] worldwide. AD usually develops in infancy, with 45% of patients developing symptoms by 6 months of age, 60% by 12 months,[1] and approximately 85% by 5 years.[1,2] Approximately 70% may have remission before adolescence, whereas 25% will continue to have AD into adulthood.[1,3] A systematic review of cross-sectional and cohort studies found that between 16% and 37% of adults report adult-onset AD.[26] Rare syndromes (eg, Wiskott-Aldrich syndrome) may present with AD.

Among a number of diagnostic approaches for AD,[27-29] Hanifin and Rajka[30] diagnostic criteria and the UK working party[31] modifications are the most widely validated and used for diagnosis (Table 1), but a consensus reference standard does not exist.[27,28,32,33] There are more than 180 different ways to classify AD.[34] Although eczema best describes itchy (pruritic), inflamed, and scaly papules and plaques (ie, primarily a morphologic description that can apply to multiple diseases such as atopic, irritant, radiation induced, or contact dermatitis), AD (atopic eczema) more accurately describes a specific disease.

AD symptoms, associated sleep disturbance, and atopic and nonatopic comorbidities contribute to patient and caregiver burden. AD negatively affects quality of life and activities of daily living with similar or worse impact compared with other chronic skin and systemic diseases.[35,36]

Intense pruritus occurs in most patients with AD, is difficult to control, and is frequently reported as the most burdensome symptom of disease.[25,37,38] More than 85% of patients with moderate-to-severe AD report daily itch and 42% experience itch for 18 or more hours each day.[39] In addition, more than 40% of children and 60% of adults with AD report skin pain, which may be associated with itch, scratching, open skin/fissures, and possibly, a neuropathic component.[40,41]

Children (47%-80%) and adults (33%-87%) frequently report sleep disturbance, with worse sleep quality in patients with severe, active disease, and consequent negative impact on daytime mood, behavior, and productivity.[42,43] Subjective sleep problems include difficulty falling asleep, frequent nighttime wakening and, compared with controls, excessive daytime sleepiness.[43] Objective findings include prolonged sleep-onset latency, reduced sleep efficiency, and increased time awake.[43] Sleep disturbance is likely driven by itching and scratching which is more difficult to suppress at night.[44]

Owing to AD, patients frequently report activity limitations and self-consciousness about the appearance of their skin, leading to avoidance of social interactions.[25,45] Caregivers of pediatric patients with AD report frequent sleep disturbance, co-sleeping, exhaustion, worry, and social isolation related to the child's AD, with greater family burden associated with more severe disease.[46-49]

Pathophysiology and Mechanisms Overview

The pathogenesis of AD is complex and multifactorial[50-52] and is reflected in heterogeneous clinical phenotypes.[34] Detailed reviews of AD pathophysiology appear elsewhere,[50,53,54] including mechanism of itch (pruritus).[55-59] AD involves skin barrier defects, immune dysregulation, and environmental interactions (microbial dysbiosis, irritants, and allergens). Genetic factors such as loss-of-function mutations in the gene encoding filaggrin and acquired defects in the epidermal barrier (including filaggrin and lipids and tight junction complexes [eg, claudin-1]) predispose to increased transepidermal water loss and cutaneous dryness in AD.[60,61] The mechanism of disease involves an impaired barrier that is permissive to allergen or toxin penetration, which elicits an immune response and favors allergen sensitization. Activated keratinocytes release thymic stromal lymphopoietin (TSLP), IL-33, and IL-25, which activate type 2 innate lymphoid cells, dendritic cells, and basophils,[62] leading to an activation of T_H2 cells. New systemic therapies that specifically target these cytokines reveal the importance of major type 2 cytokines IL-4 and IL-13 in AD pathophysiology. In addition, the production of type 2-associated cytokine IL-31 promotes itching in AD. In chronic AD lesions, other identified inflammatory cell types include $T_H17/22$ and T_H1 cells. Their precise role, however, in the disease pathophysiology remains to be determined. Both skin barrier defects and the suppression of cutaneous innate immunity by type 2 cytokines lead to dysbiosis of AD skin microbiome and predispose patients to increased skin infections, predominantly due to *Staphylococcus aureus* and viruses (eg, herpes simplex viruses, molluscum contagiosum virus).[63] Although there is a strong association between *S aureus* and disease severity, and *S aureus* toxins and proteases are capable of exacerbating inflammation, the precise role of *S aureus* in AD remains unclear.[64] In addition, there is growing interest in understanding the

Table 1
Atopic Dermatitis Diagnostic Criteria as Defined by Hanifin and Rajka and as Subsequently Adapted by the UK Working Party

Hanifin and Rajka[30]		UKWP 1994[31]	
At least 3 of	Pruritus	An itchy skin condition (or parental report of scratching or rubbing in a child)	
	Typical morphology and distribution	And at least 3 of	History of involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles, or around the neck (including cheeks in children under 10 y)
	Chronic or chronically relapsing dermatitis		Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4 y)
	Personal or family history of atopy (asthma, allergic rhinitis, AD)		Personal history of asthma or (allergic rhinitis) (or history of atopic disease in a first-degree relative in children under 4 y)
And at least 3 of	Xerosis		History of general dry skin in the last year
	Ichthyosis/palmar hyperlinearity/keratosis pilaris		Onset under the age of 2 y (not used if child is under 4 y)
	Immediate (type I) skin test reactivity		
	Elevated serum IgE		
	Early age of onset		
	Tendency toward cutaneous infections (eg, *Staphylococcus aureus* and herpes simplex)/impaired cell-mediated immunity		
	Tendency toward nonspecific hand or foot dermatitis		
	Nipple eczema		
	Cheilitis		
	Recurrent conjunctivitis		
	Dennie-Morgan infraorbital fold		
	Keratoconus		
	Anterior subcapsular cataracts		
	Orbital darkening		
	Facial pallor/facial erythema		
	Pityriasis alba		
	Anterior neck folds		
	Itch when sweating		
	Intolerance to wool and lipid solvents		
	Perifollicular accentuation		
	[IgE-mediated] Food [allergy]		
	Course influenced by environmental/emotional factors		
	White dermographism/delayed blanch		

Abbreviations: AD, atopic dermatitis; UKWP, UK Working Party.

role of other commensal skin bacteria such as coagulase-negative staphylococci including *S epidimidis* and *S hominis* in AD.

Comorbidities and Complications of Atopic Dermatitis

Several comorbid atopic (food allergy, asthma, allergic rhinitis) and nonatopic (depression, anxiety, neurocognitive impairment, skin infections, and adverse effects of treatment) health problems occur in patients with AD.[65-69] AD severity is associated with developing such comorbidities and may be due to uncontrolled disease, systemic inflammation, and disturbed sleep.[70-72] Complications of skin traumatization in AD include bacterial, viral, and fungal infection, lichen simplex chronicus, and prurigo nodularis. Severe exacerbations can present as erythroderma.

Ophthalmic and ocular diseases, some potentially sight-threatening, occur as comorbidities and complications of AD, such as recurrent keratoconjunctivitis, keratoconus, and anterior subcapsular cataracts.[73-75] Conjunctivitis, for example, can occur after treatment with dupilumab, tralokinumab, or lebrikizumab.

AD is associated with increased fracture incidence[76,77] which may be due to decreased physical activity, increased systemic inflammation, and excessive use of certain treatments such as potent topical and systemic corticosteroids.[78,79] Shared mechanisms may also promote AD's possible association with cardiovascular and metabolic diseases, including obesity, hypertension, myocardial infarction, stroke, and heart failure.[80-82]

Patient and Caregiver Experience Navigating Costs and Care

Patients and families may experience significant financial burden associated with AD, including costs related to co-pays and deductibles for health care visits and prescriptions, prescription costs not covered by insurance, over-the-counter emollients and medications, and indirect financial effects such as work absenteeism and/or decreased productivity.[46,49,83] Out-of-pocket expenses are particularly important to patients and families and can affect management outcomes.[83] Recent survey data from the National Eczema Association indicate that the median annual AD out-of-pocket expense was $600; 42% of patients with AD reported greater than $1000 out-of-pocket expenses annually and 9% reported out-of-pocket expenses greater than $5000 per year. Higher out-of-pocket expenses are associated with increased disease severity and flares.[83,84]

These data also indicate that many patients with AD use, including concurrently, at least 3 prescription therapies.[84] Nearly half of all study respondents (49%) reported out-of-pocket costs for prescription medications that were not covered by insurance.

The financial burden of AD also extends beyond direct out-of-pocket costs. Caregivers of children with moderate-to-severe AD reported spending an average 20 hours per week managing the disease.[47] Caregivers consequently face tradeoffs, such as working less, working flexible hours, or leaving the workforce, to accommodate the time-intensive demands of managing AD.[46,47] Disparities in social determinants of health exacerbate these burdens.[85]

Collectively, these data indicate that there are potentially large financial and nonfinancial burdens associated with AD care for patients and families. Persons who care for patients with AD would benefit from recognition of these potential costs and burdens and engage in shared decision-making that accounts for ways to potentially minimize these burdens as part of achieving optimal AD outcomes.

Atopic Dermatitis in Diverse Skin Tones (Skin of Color): Clinical Considerations and Health Disparities

Although ethnic diversity is increasing in North America and in many other regions of the world,[86,87] race, ethnicity, and ancestry are

terms that are often confused and used incorrectly[88] in medicine and research. Historically racialized communities continue to face health disparities due to a number of factors, including structural and systemic racism.[89-92] We provide suggestions for clinicians to consider when applying our guidance on an individual-patient and population-societal level.

AD can present with different morphologies, including papular, lichenoid, nummular and follicular clinical forms,[93] and extensor surface, eyelid, and inverse flexural involvement (see https://eczemainskinofcolor.org/ and https://nationaleczema.org/eczema-skin-of-color/).[5,94,95] Classical features, such as erythema, can vary among skin tones—erythema reflects increased blood flow to superficial capillaries and if its literal Greek meaning, red, is strictly followed, the diversity of AD presentations can be importantly underappreciated.[96,97] Consistent with calls to improve representation of diverse ethnic backgrounds and skin tones in medicine[98-102] and society, we define erythema to include transient skin alterations characteristic of active AD inflammation including red, shades of brown, violaceous, or gray appearances. Postinflammatory dyspigmentation (hypo- or hyperpigmentation) may persist for months to years and be important to patients. Principles of AD care remain similar for all skin types. Hence, although there is interest in understanding potential variation in the AD inflammatory response across race, ethnicity, or ancestry,[103,104] the relevance of these findings to informing treatment selection is not clear and, so far, multiple agents display no differential treatment response across these groups. Beyond potential biological factors, social and structural factors affect patient and family diagnosis and optimal health care access and utilization.[105]

In a 2002 race-based analysis of US national ambulatory medical services, patients identified as Asian or Pacific Islander accounted for 16% of 8 million visits for AD (population adjusted odds ratio [OR] vs patients identified as White, 6.7 [95% CI, 4.8-9.5])[106] and patients identified as Black or African American accounted for 20% (adjusted OR, 3.4 [95% CI, 2.5-4.7]). Indigenous Peoples were excluded from the analysis. Furthermore, historically racialized groups face worse outcomes and inequities in access to care.[107] For example, children with AD in the United States identifying as Black or Hispanic are more likely to miss school[108] and, rather than access specialist care, use primary care and the emergency department for AD.[109] Historically racialized groups are also less likely to receive evidence-based treatments appropriate for their AD severity.[110] North American Indigenous Peoples' social determinants of health, including historical and social contexts, remote locations, crowded housing conditions on reservations, and suboptimal health care access (particularly in rural and remote areas), influence health outcomes.[111-115] Optimally addressing the racial, ethnic, and cultural diversities of Indigenous Peoples requires not only actively and equitably engaging them in research and policymaking but also incorporating culturally sensitive (eg, appreciating Indigenous Ways of Knowing[116] and research practices[117]) decision-making during individual clinical encounters.[118]

Given the complex factors driving disparities, improved research and educational initiatives alongside interdisciplinary and multistakeholder involvement are needed to help reduce gaps in care. At individual and population levels, clinicians hoping to achieve optimal AD outcomes will actively address unconscious (implicit) biases and account for patient contextual factors in shared decision-making.[89,91,119,120] Clinicians should also promote structural and organizational change.[121] Consistent with this, a major theme of the AAAAI/ACAAI JTF Atopic Dermatitis guidelines is promoting equity, diversity, and inclusiveness.

Methods—How These Guidelines Were Created

The AAAAI/ACAAI JTFPP and the Evidence in Allergy Group at McMaster University developed these guidelines. The JTFPP partnered with the Evidence in Allergy Group for their methodologic support in the development and dissemination of clinical practice recommendations to provide patients, clinicians, and policymakers with up-to-date, evidence-based, and user-friendly guidance.

Standards, Methods, and Processes for Living and Trustworthy Guidance

The guideline panel produced the recommendations following standards for trustworthy guideline development using the GRADE approach,[4,7,122,123] principles laid out by Guidelines International Network-McMaster,[124] RIGHT,[125] AGREE II,[126] and Institute of Medicine,[1,127] and in compliance with the AAAAI/ACAAI JTFPP policies. We fulfilled criteria required to report robust use of GRADE.[4] The eAppendix provides additional details.

Selection and Support of the Panel (Organization, Panel Composition, Planning, and Coordination)

The JTFPP conceived the project, obtained approvals from the parent organizations, composed the guideline workgroup of clinical experts, methodologist, and Chairs, and provided overall oversight (through a JTFPP Liaison: Dr Greenhawt), including document review, feedback, and approval of the guideline. The guideline panel, striving for equity, diversity, and inclusiveness (eg, age, gender, ethnicity, geography), included 21 individuals, of whom 12 were AD experts (dermatologists or allergy-immunology specialists or AD psychologist, many of whom were clinician-scientists), 5 were frontline clinicians (family practice, pediatrics, internal medicine, pharmacist), and 4 were either patients with AD or their caregivers. The Methods Chair (methodological and content expertise) and a Clinical Chair (content expertise) guided the panel discussions. A resource person with methods expertise (Dr Guyatt) assisted the Methods Chair, and observers (Mr Chu, Ms Zhao, Dr Chen, Dr Oykhman, Ms Bakaa) from the Evidence in Allergy Group attended the panel meetings but did not directly participate in discussions. There were 22 additional health care workers (eg, nurses, pharmacists, infectious disease specialists), patient and caregiver partners, and patient advocacy group representatives who provided counsel to the guideline panel, including prioritizing outcomes, subgroup analyses, defining thresholds of important effects, and providing data interpretation. The Evidence in Allergy Group's researchers conducted systematic reviews of evidence and coordinated the guideline development process, including use of the GRADE approach, determining methods, screening and supporting patient and clinician partners, preparing agendas and meeting materials, facilitating panel discussions, and holding focus groups with patient and family partners.

Guideline Funding and Management of Conflicts of Interest

Development of these guidelines was wholly funded by the JTFPP through the AAAAI and ACAAI, nonprofit medical specialty societies that represent allergy-immunology specialists. Most members of the guideline panel were members of the AAAAI and/or ACAAI. The JTFPP supported panel appointments, but the panel exclusively developed the recommendations.

Patient and caregiver partners were offered an honorarium by the Evidence in Allergy Group for their time and participation; otherwise, panel members did not receive payment. Some researchers who contributed to the systematic evidence reviews received grant support through the McMaster Evidence in Allergy Group and JTFPP. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed according to JTFPP policies (https://www.allergyparameters.org/parameter-and-guideline-development-process/) based on recommendations of the Institute of Medicine (now National Academy of Medicine)[127] and the Guidelines International Network.[128] Before appointment to the panel, individuals disclosed financial and nonfinancial interests. The Co-Chairs and JTFPP reviewed the disclosures and judged which

interests were conflicts and should be managed. The eAppendix provides the completed "Disclosure of Interest" forms of all panel members. The eAppendix also summarizes decisions about which interests were judged to be conflicts. At the time of appointment, most of the guideline panel, including the co-chairs, had no conflicts of interest as defined and judged by JTFPP (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). Some panelists disclosed new interests or relationships during the development process, but for any individual recommendation, most was conflict free.

When panel members had potential conflicts of interest pertaining to specific recommendations, the management process included recusal from decision-making for those recommendations. Although they were encouraged to contribute to discussions regarding the scientific evidence summaries, practical issues, and implementation considerations, panel members with a current direct financial interest in a commercial entity with any product that could be affected by the guidelines and with material intellectual (nonfinancial) conflicts were recused from making judgments about relevant recommendations.

None of the McMaster-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline-development process had any current material interest in a commercial entity with any product that could be affected by the guidelines.

Guideline Perspective, Outcomes, and Values and Preferences

The target audience for this guidance consists primarily of clinicians, but secondarily of patients, their caregivers, and health care decision-makers. The panel primarily considered an individual patient perspective but also took account of contextual factors (such as resources, feasibility, acceptability, equity) to accommodate adoption and adaptation for other contexts. During all discussions, which occurred through email and virtual meetings, the Methods Chair actively reminded the panel that guidelines should focus their main considerations for patient values and preferences representative of general patients with AD.

Panel members, including 4 patient partners who either had AD or were caregivers for individuals with the condition, considered values and preferences immediately in advance of developing each recommendation. The multistakeholder guideline panel considered a list of patient-important AD outcomes a priori, based on established methods,[129] the Harmonizing Outcomes Measures for Eczema (HOME)[37,38,130] and input from panel members, patient and caregiver partners, frontline clinicians, and partner AD advocacy organizations. At the outset of the guideline development process, they rated the importance of each outcome and whether they agreed with a hierarchy ranging from "critically important" to "not very important." Similarly, they set thresholds for trivial or unimportant effect sizes and those of small but important, moderate, and large effect sizes for benefits and harms. The Methods Chair reminded the guideline panel to make their recommendations based on the perspective of patients rather than their own values and preferences. A major source of such information was a linked systematic review addressing patient values and preferences for the treatment of AD.[20] In areas where data were lacking, other sources of information included conversations and focus groups with patient and caregiver partners and clinicians' experience in shared decision-making with patients and families.

Sources of Evidence

To create recommendations, the panel relied on evidence synthesized in systematic reviews and (network) meta-analyses[131] led by the Evidence in Allergy Group. These included the following:

1. Systematic review and meta-analysis of bleach baths vs usual baths for atopic dermatitis[16]
2. Systematic review and meta-analysis of dietary elimination vs usual diet for atopic dermatitis[17]
3. Systematic review and meta-analysis of AIT vs no AIT for atopic dermatitis[18]
4. Systematic review and meta-analysis of cancer risk with TCIs, pimecrolimus and tacrolimus, for atopic dermatitis[15]
5. Systematic review and NMA of topical treatments for atopic dermatitis—referred to here as the topicals NMA[14]
6. Systematic review and NMA of systemic treatments (monoclonal antibodies, small molecules [eg, JAK inhibitors, cyclosporine, methotrexate], UV light therapy [phototherapy]) for atopic dermatitis—referred to here as the systemics NMA[19]
7. Systematic review of values and preferences of patients and caregivers regarding treatment of atopic dermatitis[20]

Although the investigators responsible for the meta-analyses rated the certainty of the evidence, the guideline panel reassessed these ratings independently.

Additional guideline-associated publications include the following:

1. What parents should know about atopic dermatitis JAMA pediatrics patient page[5] (1-page handout)
2. Things to know about managing infant atopic dermatitis[6] (1-page handout)
3. Trustworthy patient-centered guidelines: insights from atopic dermatitis and a proposal for the future[1] (patient engagement and guideline development methods)

Evidence Review and Development of Recommendations

For each guideline question, the Evidence in Allergy Group prepared a GRADE Summary of Findings of the systematically reviewed scientific evidence and values and preferences. Panel members also identified additional potentially relevant studies.

Under the direction of the Evidence in Allergy Group, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) and GRADE guidance for conducting systematic reviews of intervention effects and values and preferences and summarized findings within Summary of Findings and Evidence-to-Decision frameworks.[7,132] The certainty in the body of evidence (also known as quality of the evidence or confidence in estimates) was assessed for each outcome of interest following the GRADE approach based on the following domains: risk of bias, imprecision, inconsistency, indirectness of the evidence, risk of publication bias, presence of large effects, dose-effect relationship, and an assessment of the effect of plausible residual and opposing confounding.[7] For network meta-analyses,[131] we also considered intransitivity[133] and incoherence.[131] Details of the GRADE approach, including definition of terms, are summarized elsewhere.[7,131,134] The certainty was categorized into 4 levels ranging from very low, low, moderate, and high with a target of certainty of non-zero effects. The systematic reviews and meta-analyses fulfilled explicit requirements for robust use of GRADE and to report its proper use.[4]

From January to June 2022, and ongoing literature review to July 31, 2023, the panel developed recommendations during 6 online meetings and through online communication. For each recommendation, the panel reached consensus on the following: the certainty in the evidence, the balance of benefits and harms, and the values and preferences associated with the decision. The panel aimed to create a recommendation based on consensus but elected, at the beginning of the first panel meeting, to call a vote if they could not reach consensus. Before discussions started, the panel determined that a simple majority would provide the direction of the recommendation and that 80% would be required to make a strong recommendation. All members of the panel reviewed and approved the final guidelines.

Table 2
Interpretation of Strong and Conditional Recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Different choices will be appropriate for individual patients; clinicians must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty of the evidence. In such instances, further research may provide important information that alters the recommendations.	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

NOTE. The Infographic summarizes the recommendations.

Document Review

All members of the panel reviewed draft recommendations, revised, and then made them available online from August 4, 2023, to September 8, 2023, for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. There were 13 individuals or organizations who submitted comments in addition to 8 peer-reviewers appointed by the AAAAI and ACAAI based on their medical content and methodological expertise. In response to pertinent comments, the panel accordingly revised the document, but no changes were made to the recommendations. On October 19, 2023, the AAAAI/ACAAI JTFPP approved that the defined guideline-development process was followed and approved publication of the guidelines.

Understanding the Recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends ...") or conditional ("the guideline panel suggests . . .") (the interpretation is found in Table 2).

How to Use These Guidelines

The JTFPP guidelines are primarily intended to help clinicians work with patients to make decisions about treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. Patients may also find these guidelines informative, in particular to facilitate discussions with clinicians. These guidelines are not intended to serve as a mandate/standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences. Decisions may be constrained by specific clinical settings and local resources, including but not limited to institutional policies, time limitations, and availability of treatments. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. AAAAI, ACAAI, the JTFPP, and the Evidence in Allergy Group do not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences, including qualifying remarks accompanying each recommendation, are integral parts and serve to facilitate a more accurate interpretation. They should never be omitted when recommendations from these guidelines are quoted or translated. Implementation of the guidelines will be facilitated by the related decision aids, summary infographic (Fig. 1), and eAppendix. The use of these guidelines is also facilitated by the explicit description of the Evidence-to-Decision frameworks and Summary of Findings tables provided or cited in references accompanying each section.

Joint Task Force American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Atopic Dermatitis (Eczema) Management Recommendations

The Infographic (Fig. 1) summarizes the recommendations.

Recommendation 1: Good practice statement: Clinicians managing all severities of atopic dermatitis should, before issuing any new therapy, (1) ensure the correct diagnosis and identify complicating diagnoses, (2) provide education, for instance an information guide about the disease[5] and an action plan, (3) address trigger avoidance, (4) ensure proper medication use/adherence, and (5) encourage application of a bland moisturizer titrated to symptomatic benefit (at least once, often multiple times, per day).

Mimickers of, and disorders complicating AD, are common and must be ruled out, such as irritant and/or allergic contact dermatitis, psoriasis, seborrheic dermatitis, photodermatoses, primary immunodeficiency disorders (inborn errors of immunity), infestations (eg, scabies), and local and systemic infections (eg, *Streptococcal, Staphylococcal*, fungal, syphilis). Inborn errors of immunity (primary immunodeficiencies) or other rare syndromes should be considered in infants and young children when there are a constellation of signs and symptoms, often multiorgan involvement with severe and/or recurrent infections or immune dysregulation, that should prompt referral. Venous stasis dermatitis and cutaneous lymphoma are more common in adults. Although it can be easily overlooked, ensuring diagnostic clarity will lead to optimal treatment of each condition.

The panel relied on existing systematic reviews and recent evidence rather than extensively reappraising the large body of literature addressing moisturizers to inform this good practice statement.[123,135,136] A 2017 systematic review of 77 RCTs including oat-, ceramide-, glycerol-, and urea-based, among other moisturizers, established that moisturizers overall improve patient-important AD outcomes.[137] Furthermore, published in 2022, a RCT of 555 children with mostly mild AD (baseline mean [SD] POEM [patient-oriented eczema measure] of 9 [6] and EASI [Eczema Area and Severity Index] 4 [4]; Table 3 presents severity strata) assigned 1:1:1:1 to any one moisturizer in the form of lotion, cream, gel, or ointment and found similar AD outcomes (POEM, EASI, flares) and adverse events among

Table 3
Some Reported Severity Strata for Measuring Atopic Dermatitis

Perspective and domain	Instrument name/design	Total score range	Number of strata	Mild	Moderate	Severe
Clinician-rated AD severity	EASI[138]	0-72	4	0.1-5	6-22	23-72
Clinician-rated AD severity Patient-rated itch, sleep disturbance	SCORAD[138]	0-103 (83 AD severity, 10 each for itch and sleep)	4[a]	10-28	29-48	49-103
Patient-rated AD severity	POEM[139]	0-28	5[b]	3-7	8-16	17-24
Patient-rated itch	VAS or NRS[140]	0-10	3	0-3	4-6	7-10
Patient-rated sleep disturbance	VAS or NRS[c]	0-10	3[c]	0-3	4-6	7-10
Patient-rated AD-related quality of life	DLQI[140] CDLQI[141]	0-30	3[d]	0-5	6-10	11-30

Abbreviations: AD, atopic dermatitis; CDLQI, Children's Dermatology Life Quality Index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index, measures signs of erythema/redness, induration/thickness, excoriation/scratching, lichenification; IGA, investigator global assessment; NRS, numeric rating scale; PGA, physician global assessment; POEM, Patient-Oriented Eczema Measure, measures in the past 7 days, patient-reported itch, sleep disturbance, bleeding, weeping/oozing, cracks/fissures, flaking, dryness/roughness; SCORAD, SCORing Atopic Dermatitis, measures similar domains as EASI and in addition, oozing/crusting, dryness, and patient-reported sleep loss, and itch; VAS, visual analogue scale.
NOTE. Strata should not be rigidly interpreted as they reflect continuums of severity[142]; reported strata vary slightly across studies (eg, EASI mild category may be reported as 1.1-7; moderate 7.1-21, and severe as >21[104]). Values lower or higher than the bands strata here represent either less severe or "clear" skin, or, vice versa, "very severe" activity. Although global assessments of severity, namely IGA or PGA, may be rapid to use to assess AD, limitations include more than 20 different definitions of IGA/PGA that hinder interpretation through a common language,[143] fair interrater reliability (intraclass correlation 0.54),[144] a focus on intensity rather than extent of disease, statistical and methodological flaws, and that the sole reliance on IGA/PGA ignores the patient perspective.[145] Although instruments such as validated IGA,[146] or product of validated IGA and body surface area,[147] may address some of these issues, extensive training and calibration, and basis in informing AD drug licensing rather than routine patient care, may limit their immediate widespread implementation in clinical practice.
[a]The original article of Kunz et al[148] describes the following 3 strata for SCORAD:
0-24 = mild
25-49 = moderate
50-103 = severe
[b]Vakharia et al[140] reported 3 strata for POEM
0-7 = mild
8-16 = moderate
17-28 = severe
[c]No direct data, values taken from itch.
[d]Original DLQI,[149] and CDLQI[150] had the following 5 strata:
Meaning of scores
0-1 = no effect at all on patient's life
2-5 = small effect on patient's life
6-10 = moderate effect on patient's life
11-20 = very large effect on patient's life
21-30 = extremely large effect on patient's life.

all 4 groups.[151] Together, these data suggest that the best moisturizer is the one that patients will use regularly. These would optimally be bland ones (free of common allergic contact dermatitis allergens),[152] and shared decision-making should express the potential tradeoffs between benefits (eg, perhaps greater benefit with ointment-based moisturizers for more severe disease) and cost, acceptability, and accessibility. A 2019 narrative review,[153] and associated infographic (https://www.bmj.com/content/367/bmj.l5882/infographic), may be helpful to patients and clinicians to address practical issues and implementation considerations. Promoting this good practice statement aligns with patient values and preferences for a strong patient-provider relationship.[20]

Educational interventions such as eczema action plans can support self-management and self-efficacy and improve disease control. Structured education programs for patients and caregivers, supported by a systematic review of 8 RCTs,[154] and up-to-date written action plans[155] are valued,[156,157] may improve outcomes,[158-161] and boost confidence.[155] Digital internet-based tools, as revealed in Eczema Care Online's 2 randomized trials published in 2022,[162] hold promise.

Topical Treatments

With AD being an immune-driven disease, patients will require anti-inflammatory treatment. Although moisturization alone may achieve this goal in the mildest of patients, and can help improve AD severity and time-to-flare in those with more severe disease, almost all patients will require a prescription anti-inflammatory treatment. Classes of such treatments include the following: prescription moisturizers (marketed as medical devices), TCS, TCIs, topical phosphodiesterase 4 inhibitors (PDE4is), topical Janus kinase (JAK) inhibitors, and topical antimicrobials. How the medication is applied can vary by the number of applications per day or whether it is applied under occlusion (eg, wet wraps). Once initial control of disease is achieved, maintaining control can vary by how frequently topical treatments should continue to be applied. Other considerations include age and location (eg, scalp, face, or folds). The eAppendix provides practical information about considering and implementing each topical treatment.

Treating Uncontrolled Atopic Dermatitis (Induction of Remission)

The use of topical medications for AD treatment can be conceptualized into 2 phases (Fig 2): (1) treatments for uncontrolled disease (active disease, also referred to as flares), or otherwise referred to as induction of remission, and (2) intermittent therapy to treat subclinical inflammation and prevent a future flare, also called maintenance (of remission) therapy.[163] Another term for regular use of topical treatments to prevent a future flare is proactive therapy.

The next section presents recommendations for topical prescription treatments for induction of AD remission.

Question 1a. Which topical treatments should be used to treat active AD disease (induction of remission)?

Prescription Moisturizers

These are registered and marketed as prescription medical devices and have not undergone the same FDA drug regulatory process as most of the other prescription treatments that appear in the other topical treatment sections.

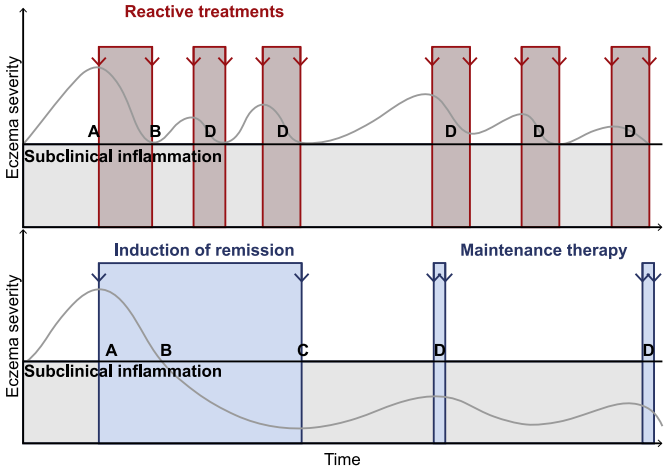

Figure 2. Concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis. Diagram (top) illustrates what might happen when AD treatment ceases once signs and symptoms have superficially reduced (the period from point A to point B) as opposed to what might happen (bottom) if initial treatment is extended to clear subclinical disease (point C). Induction of remission is followed by maintenance treatment with 2 consecutive days of treatment per week to previously active sites (points D). Maintenance therapy is at regular intervals and not specifically when "flares" are beginning to occur. Figure from Tang et al.[163]

Recommendation 2: In patients with atopic dermatitis, the JTF panel suggests using a standard, bland (free of fragrance and other potential contact allergens) over-the-counter moisturizer over a prescription moisturizer medical device (eg, Atopiclair, Eletone, Epiceram, MimyX, Neosalus, Zenieva, and PruMyx) (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Different moisturizers (either prescription or over-the-counter) have different odors and textures/consistency that may importantly influence decision-making.
2. Patients with an insurance plan that covers the cost of prescription moisturizer, or those that otherwise can easily absorb the direct cost, and who place a higher value on the small potential benefits of prescription moisturizers over their costs, burdens, and lower accessibility may prefer them vs over-the-counter ones.
3. Patients who have not improved sufficiently with routine use of standard over-the-counter moisturizers may prefer a trial of prescription moisturizer before adding better proven topical anti-inflammatory medications (see next recommendations).

Benefits and Harms: The systematic review and NMA of all topical prescription treatments,[14] including 9 RCTs involving various prescription moisturizers (approximately 400 patients), revealed that compared with standard moisturizers in patients with mild-moderate AD, prescription moisturizers probably improve AD severity slightly (reduction by 50% within 2-6 weeks in 18% with standard moisturizer vs 24% with prescription moisturizer; absolute RD 6% [95% CI, −3% to 16%]) and probably slightly improve flares (10% with standard moisturizer vs 4% with prescription moisturizer; RD −6% [95% CI, −9 to −1]). Certainty was lower for itch and safety outcomes, prescription moisturizers may improve itch (50% reduction from baseline in 26% with standard moisturizers vs 51% with prescription moisturizer; RD 25% [15% to 36%]) and have little to no difference in adverse events (15% vs 14% for any adverse event and 3% vs 2% for adverse events causing discontinuation). No study addressed AD-related quality of life or sleep disturbance.

Values and Preferences: The linked systematic review,[20] along with direct patient and caregiver input addressing their perspectives of prescription and over-the-counter moisturizers, revealed that many patients with AD prefer odorless treatments that are not visible and have a low impact on daily life; that they value nonpharmacologic therapies; and that they also value the texture or sensation of moisturizer on the skin.

Given the close balance between the 2 possible treatment alternatives, the panel inferred that most well-informed patients placed a higher value on avoiding burdens, inconvenience, and cost that are more likely to be the case with prescription moisturizers (eg, having to obtain or refill a prescription and/or check insurance coverage frequently; that the amount of prescription moisturizer per refill may be importantly smaller than that which can be obtained over-the-counter [eg, tubs]; having to address these issues during travel or in time-sensitive scenarios). Some panelists shared that some prescription moisturizers may have a stronger odor and different texture compared with some over-the-counter moisturizers but recognized that this could vary among moisturizers.

Contextual Factors: The cost of prescription moisturizers is generally higher than the cost of over-the-counter moisturizers. Although costs can vary substantially, especially depending on whether they are being paid for out-of-pocket, the scope of insurance coverage, and by pharmacy, it is common for prescriptions to range from $100 for a 100 g tube to $1000 or more (eg, GoodRx on January 1, 2023, lists that Epiceram retails at $6826 for a 90 g tube, Atopiclair retails at $86 retails for a 100 g tube, Eletone retails at $306 for a 100 g tube, Neosalus retails at $177 for a 100 g tube, PruMyx retails at $137 for a 140 g tube; clinical experts, however, shared that some of their insured patients reported paying $20 for some prescription moisturizers from certain pharmacies). The available size of prescription moisturizer tubes is often much smaller compared with available over-the-counter ones.

Summary of Rationale: The panel inferred that most well-informed patients with AD would value avoiding the potential inconvenience, burdens, practical implications, and cost of a prescription moisturizer than its moderate certainty for small benefits in 2 important outcomes, low certainty for larger improvements in itch, and no available data on quality of life. Hence, the panel inferred that most patients with AD would first want to try over-the-counter moisturizers, if they are not doing so already (see Good Practice Statement). A few patients (see conditions to consider) might prefer prescription moisturizers compared with over-the-counter ones. The low-certainty evidence and close balance of benefits vs harms and burdens drove the conditional recommendation.

Topical Corticosteroids

Recommendation 3: In patients with uncontrolled atopic dermatitis refractory to moisturization alone, the JTF panel recommends addition of a topical corticosteroid over no topical corticosteroid (strong recommendation, high-certainty evidence)

Benefits and Harms: The linked systematic review and NMA synthesized 219 RCTs enrolling 43,123 infants, children, and adults with primarily mild-moderate AD addressing 68 different treatments.[14] Figure 3 presents the summary of findings across outcomes. Few studies compared the effects of TCS by location of the body (eg, head and neck vs rest of body), albeit those that did suggested similar treatment effects across body parts.

TCS, used in RCTs mostly for 2 to 6 weeks, probably did not importantly increase adverse effects, including skin infections, atrophy, or other local skin changes. A Cochrane systematic review made similar conclusions, reporting 26 cases of skin atrophy of 3574 RCT children and adult participants applying mild, moderate, and potent TCS for primarily either 1 to 6 weeks or 16 to 20 weeks (raw proportion: 7 per 1000 [95% CI, 5-11 per 1000]).[164]

Values and Preferences: The linked systematic review[20] along with direct patient and caregiver input revealed that patients with AD prefer to use nonprescription therapies before TCS, use TCS for the

		Atopic Dermatitis Severity SCORAD (0–103)	Itch NRS (0–10)	Sleep Disturbance NRS (0–10)	Eczema-Related Quality of Life DLQI (0–30)	Atopic Dermatitis Flare	Any Adverse Event	Discontinuation due to Adverse Event
		MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CrI)	RD (95%CrI)	RD (95%CrI)
Baseline		25.96	5.40	4.89	9.43	95 per 1000	305 per 1000	28 per 1000
JAK Inhibitors								
Delgocitinib Cream		-5.64 (-8.36 to -2.91)						
Delgocitinib Ointment		-9.98 (-13.81 to -6.15)	-1.47 (-2.17 to -0.77)		-7.41 (-10.16 to -4.66)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
Ruxolitinib		-4.82 (-5.65 to -4.00)	-2.11 (-2.96 to -1.26)	-0.57 (-1.15 to 0.02)	-4.82 (-6.35 to -3.44)	-74 (-84 to -51)	-37 (-93 to 25)	-21 (-25 to -15)
PDE4 Inhibitors								
Crisaborole		-4.89 (-8.69 to -1.08)	-0.64 (-1.11 to -0.15)		-1.23 (-2.34 to -0.09)	-59 (-81 to -12)	43 (-32 to 124)	9 (-15 to 58)
Difamilast		-5.41 (-9.12 to -1.68)	-1.26 (-2.09 to -0.42)		-1.55 (-3.00 to -0.03)	-45 (-71 to 2)	-41 (-110 to 39)	-17 (-22 to -9)
Lotamilast		-2.89 (-8.84 to 3.06)	0.04 (-1.53 to 1.62)			-23 (-80 to 196)	6 (-153 to 211)	-10 (-25 to 28)
Roflumilast		-2.15 (-4.20 to -0.12)	-1.55 (-3.39 to 0.29)				177 (-38 to 408)	23 (-27 to 367)
Topical Calcineurin Inhibitors								
Pimecrolimus		-7.23 (-8.76 to -5.72)	-1.61 (-2.00 to -1.21)	-2.13 (-3.15 to -1.01)	-1.44 (-2.38 to -0.62)	-53 (-66 to -39)	21 (-15 to 59)	-11 (-16 to -3)
Tacrolimus 0.1% (High Dose)		-13.05 (-15.15 to -10.95)	-2.27 (-2.84 to -1.70)		-3.65 (-5.59 to -1.83)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Tacrolimus 0.03% (Low Dose)		-9.38 (-11.22 to -7.55)	-1.97 (-2.44 to -1.50)	-0.17 (-1.97 to 1.60)	-1.72 (-3.47 to -0.02)	-70 (-85 to -41)	29 (-18 to 79)	-15 (-19 to -10)
Topical Corticosteroids								
Conventional TCS Potency: High	TCS Group 1	-17.81 (-21.32 to -14.30)	-2.34 (-4.37 to -0.32)				-96 (-179 to 11)	-25 (-27 to -18)
	TCS Group 2	-13.82 (-18.74 to -8.89)	-3.39 (-5.02 to -1.76)				-16 (-278 to 479)	
Medium (Mid)	TCS Group 3	-11.57 (-14.80 to -8.37)	-2.37 (-3.18 to -1.57)	-0.22 (-2.23 to 1.72)	-1.23 (-3.71 to 1.17)	-11 (-83 to 312)	-62 (-138 to 24)	-12 (-23 to 9)
	TCS Group 4	-12.26 (-15.02 to -9.50)	-2.62 (-3.26 to -1.98)		-5.96 (-8.53 to -3.56)	-66 (-92 to 49)	-76 (-142 to -1)	85 (-15 to 381)
Low	TCS Group 5	-8.46 (-10.90 to -6.03)	-2.09 (-2.54 to -1.64)	-0.92 (-2.57 to 0.71)	-3.82 (-6.21 to -1.44)	-83 (-92 to -57)	-102 (-138 to -63)	-18 (-23 to -12)
	TCS Group 6/7	-4.68 (-7.10 to -2.29)	-1.33 (-1.89 to -0.76)	0.32 (-1.51 to 2.10)	-1.48 (-3.38 to 0.34)	-13 (-78 to 234)	-33 (-105 to 47)	-6 (-18 to 13)
Other								
Antibiotic		-1.48 (-6.77 to 3.81)	-0.32 (-2.15 to 1.51)		-1.33 (-3.35 to 0.69)	-56 (-94 to 499)	50 (-153 to 306)	229 (-5 to 834)
Prescription Moisturizers		-1.94 (-4.83 to 0.95)	-1.63 (-2.28 to -0.97)			-60 (-82 to -5)	-8 (-111 to 111)	-10 (-23 to 17)
Tapinarof		-11.26 (-16.55 to -6.03)	-1.93 (-2.99 to -0.89)			-64 (-88 to 20)	155 (19 to 299)	-14 (-23 to 9)

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from control	Possibly not clearly different from control

Figure 3. Summary of comparative effects of topical treatments on patient-important outcomes for controlling atopic dermatitis. The certainty of the evidence was rated by the GRADE criteria. We categorized the interventions according to a minimally contextualized framework with a target of certainty of a non-zero effect. The effectiveness categories depict the magnitude of effect, whereas the certainty of the evidence presents whether the estimated effect is trustworthy or not. Detailed individual categorizations of all 68 analyzed interventions are presented in the associated systematic review.[14] Analyses updated to October 7, 2023 produced similar findings. CrI, credible interval; MD, mean difference; RD, risk difference.

minimum amount of time possible, and would place a high value on rapidly relieving itching or burning skin sensations.

Contextual Factors: The panel inferred that TCSs are accessible and feasible to use.

Summary of Rationale: The panel inferred that most well-informed patients would value the certain benefits and harms for multiple classes of TCS.

Implementation Considerations: TCS are classified in multiple ways —1 to 7 in the US system with 1 representing the most potent. The linked systematic review and NMA (topical NMA)[14] revealed that the US system (Table 4) is best used in research but that, in clinical practice, there are effectively 4 classes of potency of topical treatments (Fig 3). Hence, both systems must be known to interpret and apply the literature.

Exactly which TCS to use depends on a patient's previous treatment history, site of application, cost, accessibility, and values and preferences.

Avoid high-potency (classes 1 and 2) TCS for prolonged periods of time (>4 weeks) and limit its use on sensitive areas (face, folds, groin)—rare instances of atrophy, telangiectasia, and striae may be more likely to occur in these areas. Continuous and prolonged use of low-potency TCS on sensitive areas can also cause these effects. Prescribing more than one potency of topical treatment to be used at different sites of the body, or depending on the severity of AD activity, must be balanced against the potential for polypharmacy to increase confusion, cost, and patient and family burden, albeit these barriers might be mitigated with clear action plans (see Good Practice Statement). The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts. After addressing active disease ("gaining control" or "inducing remission"), see the associated Recommendation 10 for continued intermittent therapy to prevent future flares ("keeping control," "maintenance of remission," or "proactive therapy").

Question 1b. Are topical calcineurin inhibitors effective and safe for atopic dermatitis when compared with topical corticosteroids?

Topical Calcineurin Inhibitors (Topical Pimecrolimus and Tacrolimus)

Recommendation 4: In patients aged 3 months or older with uncontrolled atopic dermatitis refractory to moisturization alone, the JTF panel recommends addition of a topical calcineurin inhibitor (pimecrolimus, tacrolimus) over no added topical calcineurin inhibitor (strong recommendation, high-certainty evidence).

Table 4
List of Some Available Topical Corticosteroids

Potency group	Corticosteroid	Concentration (%)	Formulation	Coopman classification
Group 1 (highest)	Augmented betamethasone dipropionate	0.05	Ointment, gel, lotion	D1
	Clobetasol propionate	0.05	Ointment, cream, gel, lotion	D1
	Fluocinonide	0.1	Cream	B
	Halobetasol propionate	0.05	Ointment, cream, lotion, foam	
Group 2 (high)	Amcinonide	0.1	Ointment	D2
	Betamethasone dipropionate	0.05	Ointment, augmented cream	D1
	Clobetasol propionate	0.025	Cream	D1
	Desoximetasone	0.25	Ointment, cream, spray	C
		0.05	Gel	
	Diflorasone diacetate	0.05	Ointment, cream	D1
	Fluocinonide	0.05	Ointment, cream, gel, solution	B
	Halcinonide	0.1	Ointment, cream, solution	B
	Halobetasol propionate	0.01	Lotion	
Group 3 (medium-high)	Amcinonide	0.1	Cream, lotion	B
	Betamethasone dipropionate	0.05	Cream	D1
	Betamethasone valerate	0.1	Ointment	D1
		0.12	Foam	
	Desoximetasone	0.05	Ointment, cream	C
	Diflorasone diacetate	0.05	Cream	D1
	Fluocinonide emollient	0.05	Cream	B
	Fluticasone propionate	0.005	Ointment	D1
	Mometasone furoate	0.1	Ointment	D1
	Triamcinolone acetonide	0.5	Ointment, cream	B
Group 4 (medium)	Betamethasone dipropionate	0.05	Spray	D1
	Clocortolone pivalate	0.1	Cream	C
	Fluocinolone acetonide	0.025	Ointment	B
	Fluticasone propionate	0.05	Cream	D1
	Hydrocortisone valerate	0.2	Ointment	A
	Mometasone furoate	0.1	Cream, lotion, solution	D1
	Triamcinolone acetonide	0.1	Ointment, cream	B
		0.05	Ointment	
Group 5 (medium-low)	Betamethasone dipropionate	0.05	Lotion	D1
	Betamethasone valerate	0.1	Cream	D1
		0.05	Ointment	
	Desonide	0.05	Ointment	B
	Fluocinolone acetonide	0.025	Cream	B
	Fluticasone propionate	0.05	Lotion	D1
	Hydrocortisone butyrate	0.1	Ointment, cream, lotion, solution	D2
	Hydrocortisone valerate	0.2	Cream	D2
	Prednicarbate	0.1	Ointment, cream	D2
	Triamcinolone acetonide	0.025	Ointment	B
		0.1	Lotion	
Group 6 (low)	Alclometasone dipropionate	0.05	Ointment, cream	D1
	Betamethasone valerate	0.1	Lotion	D1
		0.05	Cream	
	Desonide	0.05	Cream, gel, lotion, foam	B
	Fluocinolone acetonide	0.01	Cream, solution, shampoo	B
	Triamcinolone acetonide	0.025	Cream, lotion	B
Group 7 (lowest)	Hydrocortisone base	2.5	Ointment, cream, solution	A
		2	Lotion	
		1 (OTC)	Ointment, cream, gel, lotion, spray	
		0.5 (OTC)	Ointment, cream	

Abbreviations: NMA, network meta-analysis; OTC, available over-the-counter (without a prescription).
NOTE. Classified according to the US system (1 to 7, with 7 being lowest potency). The linked topical treatments systematic review and NMA[14] (Fig 3) reveal that the 7-class system is, at least, needed for research and synthesizing the evidence. Application of the findings to clinical practice produces 4 main categories of effectiveness. Hence, using the 7 classes and its effective 4 groupings are required to be known. Clobetasone butyrate 0.05% is used outside of North America and is classified among group 5 (intermediate inferior, or medium-low potency).[14] The groupings reflect a continuum and should not be interpreted rigidly. Hence, different resources may slightly vary in classification and instead, and evidence-based classification from the linked systematic review may be useful. The Coopman-Matura classification is one approach to grouping topical corticosteroids according to their molecular structure and potential for patch test cross-reactivity for suspected corticosteroid contact dermatitis. Table summarizing multiple sources including the linked systematic review with expert input,[14] NIH National Library of Medicine DailyMed,[165] Drugs@FDA,[166] UpToDate,[167] and other reviews.[168-171]

Benefits and Harms: Figure 3 summarizes the effects of TCIs for AD,[14] including the following:

- Pimecrolimus efficacy across multiple AD outcomes is intermediate between TCS 5 and TCS 6/7
- Tacrolimus 0.03% is similar to TCS 5
- Tacrolimus 0.1% is similar to TCS 4
- Combination use of TCI and TCS might lead to slightly larger benefits compared with using either TCS or TCI alone (low certainty).
- Few studies compared the effects of TCIs by location of the body (eg, head and neck vs rest of body), albeit those that did suggested similar treatment effects across body parts.

Select review of studies of animals exposed to supraphysiological doses of systemic calcineurin inhibitors, extrapolation from systemic use among patients after organ transplant, and data from uncontrolled voluntary reporting systems led the FDA to add a boxed

Table 5
Example of Some Available Topical Treatment Sizes and Costs in USA (Cost Plus Drugs April 2023)

Medication (generic name)	Concentration	Brand name	Form	Amount	Retail price	Direct purchase price	Amount	Retail price	Direct purchase price
Triamcinolone acetonide	0.10%	Aristocort A	Ointment	15 g	$9.68	$4.97	454 g cream jar ($18.66 for ointment)	$35.79	$13.39
Triamcinolone acetonide	0.50%	Triderm	Cream	15 g	$11.89	$6.27	454 g jar	$40.85	$14.30
Triamcinolone acetonide	0.50%	Kenalog	Ointment	15 g	$16.78	$7.66	60 mL lotion (0.1% or 0.025%)	NA	NA
Augmented betamethasone dipropionate	0.05%	Diprolene augmented	Cream	15 g	$23.64	$5.03	50 g	NA	$6.80
Augmented betamethasone dipropionate	0.05%	Diprolene augmented	Ointment	15 g	$44.43	$12.92	NA	NA	NA
Hydrocortisone	1%	Preparation H	Cream	28.4 g	$25.57	$4.49	NA	NA	NA
Betamethasone dipropionate	0.05%	Alphatrex	Cream	15 g	$33.32	$7.63	45 g	$74.72	$18.50
Mometasone furoate	0.10%	Elocon	Cream	45 g	$50.19	$12.15	45 g ointment	$50.45	$11.41
Mupirocin	2%	Bactroban	Ointment	22 g	$51.56	$5.25	NA	NA	NA
Fluocinonide	0.05%	Lidex	Cream	30 g	$53.42	$16.29	60 mL solution or 60 g ointment	NA	NA
Fluticasone propionate	0.05%	Cutivate	Cream	60 g	$55.80	$14.94	NA	NA	NA
Triamcinolone acetonide	0.10%	Oralone	Paste	5 g	$72.04	$18.78	NA	NA	NA
Clobetasol propionate	0.05%	Temovate	Cream	15 g	$78.33	$4.78	Foam, lotion, gel, ointment (max 60 g; 118 mL)	$90.81 to 365.30	$14.69 to 50.97
Hydrocortisone valerate	0.20%	Westcort	Cream	15 g	$83.45	$7.02	NA	NA	NA
Fluocinolone acetonide body	0.01%	Derma-smoothe/FS Body	Oil	118.28 mL	$103.99	$24.85	NA	NA	NA
Halobetasol propionate	0.05%	Ultravate	Cream	50 g	$169.75	$26.59	50 g ointment	$200.50	$30.57
Tacrolimus	0.10%	Protopic	Ointment	30 g	$182.67	$35.20	100 g	$676.45	$71.34
Clobetasol propionate emollient	0.05%	Temovate E	Cream	60 g	$219.99	$23.18	NA	NA	NA
Crisaborole	2%	Eucrisa	Ointment	60 g	$652.20[a]	NA	NA	NA	NA
Ruxolitinib cream	1.5%	Opzelura	Cream	60 g	$2410[b]	NA	NA	NA	NA

Abbreviations: NA, not applicable; TCI, topical corticosteroid.
[a]Additional examples, including additional TCIs and crisaborole, are available from The Medical Letter on Drugs and Therapeutics and reflect wholesale acquisition costs in 2020.[170,171]
[b]As of April 2023, the GoodRx price for a 60 g tube of ruxolitinib cream costs $2410 at Walgreens (and similarly priced at 9 other retailers). In general, generic drugs may be less expensive than corresponding brand-named drugs. The exact direct costs to patients may vary by individual insurance plan.

warning[172] to TCIs in 2006 and 2011 associating them with cancer. In contrast, a linked systematic review of all randomized and observational evidence, and incorporating patient values and preferences, revealed no credible increase in cancer with a broad range of typical TCI use among infants, children, and adults (4.56 per 1000 incidence across all ages without TCIs vs 4.70 per 1000 with TCIs).[15] Minor harms of TCIs include local irritation/burning.

Although the panel has individually recommended TCS and TCI vs no added anti-inflammatory, the combination of TCS with TCI has low certainty for modest added benefits than using either agent alone,[14] and the panel may address this, including when to start with a TCS vs a TCI, as a formal recommendation in the future (see Implementation considerations for how clinical experts use both types of treatment).

Values and Preferences: The panel inferred that the treatment benefits and little to no harms aligned with patient values for safe and effective medications, including alternatives to or complementary with TCS, with otherwise minimal impact on daily activities.

Contextual Factors: TCIs are available widely throughout North America. Pimecrolimus is approved for ages 3 months and older in Canada and ages 2 years or older in the United States. In both countries, tacrolimus 0.03% is approved for ages 2 years and older and tacrolimus 0.1% is approved for ages 16 years and older.

Summary of Rationale: The panel inferred that most well-informed patients would value the certain patient-important benefits and safety of using TCIs.

Implementation Considerations: A 1039 participant survey-based RCT addressed conveying how application of topical medications will feel. It revealed that positive framing, for example, a "cooling sensation and that this is a sign the medication is working" may increase acceptability of topical medications for AD. This framing proved superior to stating that there will be no adverse effects or framing them as "painful" (eg, burning), "stinging," or cooling alone (willingness to use on scale of 1-9, higher being more willing, with counseling about potential sensation and it is a signal of efficacy mean [SD] 6.9 [1.8], with counseling about potential sensation alone 5.3 [1.9], and with no counseling 4.4 [1.9]).[173] Other potential strategies include cooling the tube, such as in a refrigerator, applying it after moisturizing, or applying it after initially using TCS for a few days.

By considering patient values and preferences and the adverse effect profile of TCS and TCI, clinicians might usually use TCS or TCI for different body sites. For example, TCS for the general body and TCI for more sensitive areas such as face and folds. Although both TCS and TCI likely have patient-important benefits and little-to-no harms, clinicians should consider that TCS generally come in larger dispensing sizes compared with TCI (eg, 454 g tubs vs 100 g tubes) that might be more convenient and cost-effective for patients. Table 5 provides an example of some available sizes and costs as of April 2023. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Modifications to Using Topical Corticosteroids or Topical Calcineurin Inhibitors

Topical Corticosteroids Under Occlusion (Wet Wraps) vs Standard Nonocclusive Application

Temporarily applying TCS under occlusion is another method of treating localized recalcitrant lesions and is often referred to as wet wrap therapy because wet (damp) clothing or dressings are used to occlude the applied TCS.[11,174]

Recommendation 5: In patients with localized uncontrolled atopic dermatitis refractory to mid-high–potency topical treatment (US classes 2-5 or tacrolimus), the JTF panel suggests addition of a time and body area-limited (eg, 4-7 days; minimum 1 hour to maximum overnight, once per day) trial of occlusive low-mid–potency topical corticosteroid (US classes 3-7) therapy

over continued standard topical therapy alone (conditional recommendation, very low-certainty evidence)

Conditions to consider:

1. Resources and time to become educated, including the possibility of in-clinic demonstration, about the process and practicalities of efficiently and safely applying wet wraps.
2. Location of AD lesions (sensitive areas may be more challenging or burdensome to wrap, and therefore patients may be less likely to tolerate it).
3. The feasibility of wet wrap therapy fitting into the patient's schedule and daily routines.
4. Those patients with more extensive disease or relapsing generalized lesions may prefer systemic therapy instead.

Remark: In particular when there are refractory localized lesions, consider all 5 steps of the Good Practice Statement before intensifying therapy. Our clinical experts and patient partners found that applying overnight is usually the most convenient, but that sometimes applying for a shorter duration during the day can be more convenient.

Benefits and Harms: The systematic review identified 8 small RCTs, most of which published their data in only abstract form with only narrative description of tests of between group statistical significance rather than quantitative outcome data, leaving 3 small RCTs with a total sample size of 53 patients yielding very uncertain information addressing benefits or harms.[14] Therefore, the RCT evidence alone did not sufficiently inform benefits and harms.

Experiential evidence from patients and clinicians suggested that, when used judiciously for specific, local treatment of lesions in a time-limited fashion, most patients experience rapid resolution of AD lesions refractory to corresponding topical treatment without temporary occlusion. Harms include the potential for local irritation such as maceration and folliculitis. To date, no RCTs address the efficacy and safety of wet wraps using TCIs or other topical treatment classes under occlusion.

Values and Preferences: Although whole-body applications of wet wrap therapy may be burdensome for patients and families and therefore not align with most people's values, the panel inferred that most patients would value a local, time-limited wet wrap therapy intended to treat acute local lesions because they could provide a rapid and large response, patients' familiarity with the routine, and potential for self-efficacy and empowerment by using wet wraps to modify TCS that a patient is likely to already have. The panel acknowledged, however, that some patients, especially those who have more widespread disease, may prefer to pursue other therapies such as systemic agents instead of wet wrap therapy.

Contextual Factors: Wet wraps can be easily implemented using common household materials, including pajamas or old clothes/socks for hands, and existing topical treatments. The panel inferred that resources in terms of time and education are likely important to empower patients to be able to confidently and efficiently apply wet wrap therapy for acute AD flares. We supply a number of these practical tips in the associated implementation section and eAppendix.

Summary of Rationale: The panel inferred that most well-informed patients would value the ability for themselves to step up therapy to address flares refractory to standard topical treatment, with potential but uncertain large improvements in patient-important outcomes than the minor burdens and uncertain minor harms, compared with standard nonocclusive application.

Implementation Considerations: If wrapping overnight, ensure that the wrap is not constrictive.

Publications[174,175] and online educational resources[176] (eg, https://nationaleczema.org/eczema/treatment/wet-wrap-therapy/) are available and may provide a helpful overview. In-person training and demonstration are likely important to instill confidence and empower patients to effectively and efficiently use wet wrap therapy. The eAppendix provides additional practical information and implementation considerations in1-2 page handouts.

Once Daily vs Two or More Times Per Day Application of Topical Corticosteroids or Topical Calcineurin Inhibitors

Recommendation 6: In patients with uncontrolled atopic dermatitis using mid-to high-potency topical treatments (tacrolimus, topical corticosteroid US classes 1-5), the JTF panel suggests applying the medication once per day over twice per day (conditional recommendation, moderate certainty evidence).

Conditions to consider:

1. Patients who value a simpler treatment routine and using less overall medication may prefer once per day application than twice per day application.
2. Patients with a more severe flare or who might value resolving it more quickly may prefer twice per day application than once per day application.
3. Patients who value a twice per day skin care routine, or who respond better to twice per day use, than once per day, may prefer the twice daily application.

Benefits and Harms: Nine RCTs comprising 1507 participants evaluated twice per day application of TCS (US classes 1-5) or tacrolimus compared with once per day.[14] They provided high-certainty evidence for a small difference between regimens (MD −3.33 [−4.28 to −2.39] on SCORAD scale 0-103; RD to improve by 50% from baseline 5 more per 100 [1-9 more]). This is just above the a priori threshold of 3 per 100 set by the guideline panel. Twice per day application, compared with once daily application, similarly slightly improved other outcomes (itch, quality of life, sleep disturbance) with moderate or high certainty. Harms were no different between groups.[14]

Values and Preferences: The systematic review of values and preferences[20] found that patients value interventions that minimized impact on daily activities and use of medications, particularly TCS, as much as possible. The panel inferred that once per day application would align with these values, though there may be situations where patients might prefer to use twice per day (see conditions to consider).

Contextual Factors: Once per day application would use less overall TCS and TCI and could lead to less resource use compared with twice per day application.

Summary of Rationale: As the initial approach to address active eczematous lesions, the panel inferred that most well-informed patients would value the greater convenience and lower resource use of once per day application than the moderate certainty for a small, potentially unimportant, larger chance in achieving AD control with twice per day application. The potential for variability in patient values and preferences and their dynamic nature over time (eg, when facing more severe flares) drove the conditional recommendation.

Implementation Considerations: Tailoring frequency of application to patient values and preferences and empowering them to step up frequency of therapy as needed could help promote self-efficacy. The eAppendix provides additional practical information about implementation considerations in 1-2 page handouts.

Topical Phosphodiesterase 4 Inhibitors

Although many topical PDE4 inhibitors are in development[14], only crisaborole is currently available.

Recommendation 7: In patients with mild-moderate atopic dermatitis refractory to moisturization alone, the JTF panel suggests adding topical crisaborole 2% ointment over usual care alone (conditional recommendation, high-certainty evidence).

Conditions to consider:

1. Adverse effects might be more prominent when applied to sensitive areas and patients might favor another therapy with larger certain benefits and less harms compared with crisaborole.
2. The severity of AD - the small benefits found primarily in studies of patients with mild AD favor use only to treat mild AD flares. Conversely, its less certain and likely smaller benefits in more severe AD suggest against its use in more severe cases.
3. Patients who highly value noncorticosteroid treatments might place higher value on PDE4 inhibitors over the larger and high-certainty benefits in achieving AD control and little to no harm with other treatments such as TCS or TCI.

Benefits and Harms: The topical treatments NMA,[14] including 5 randomized trials and more than 2000 participants (including 2 trials comparing crisaborole to either TCS 5 or pimecrolimus), addressing crisaborole revealed small improvements in achieving AD remission (clinical severity [improving by 50% or more, RD 17 more per 100 (3 to 33 more)], itch [RD 9 more per 100 (3 fewer to 23 more)], and quality of life [RD 9 more per 100 (1 to 17 more)]) and reducing the chance of flare (6 fewer [9 to 1 fewer]). These were offset with an increase in adverse events, primarily local irritation with sensation of stinging and burning (RD 6 more per 100 [4 fewer to 21 more]). No data addressed crisaborole's impact on sleep disturbance (Fig 3). In summary, its effects in improving most patient-important AD outcomes are similar in potency to TCS 6/7.

Values and Preferences: The panel inferred that adding crisaborole, compared with standard care with a moisturizer alone, would align with patient values and preferences for alternative noncorticosteroid topical treatments and stepping up treatment as needed, but might not fully align with the desire to avoid adverse events.

Contextual Factors: Crisaborole is available across North America.

Summary of Rationale: The panel inferred that many well-informed patients would value the benefits, albeit small, for crisaborole than standard treatment with a moisturizer alone but that an appreciable number of patients would prefer to avoid the harms and burdens associated with crisaborole and prefer more effective and tolerable therapies. The close balance of benefits and harms along with variability in patient values and preferences drove the conditional recommendation.

Implementation Considerations: As described in the TCI recommendation, framing the potential for adverse effects may prepare and help enhance willingness to continue the treatment despite local irritation.[173] Applying in small quantities to a test area, particularly for sensitive areas of the body, may be helpful to evaluate the magnitude of adverse effects and its potential tolerability before wider usage.

Similar to the recommendations for TCI or TCS, prescribing multiple agents for patients to use for different levels of AD severity or application to different body sites must take into account the potential burdens and downsides of polypharmacy. Although the panel did not yet render an official recommendation for TCS or TCI vs crisaborole, many clinical experts and patients will start with TCS or TCI first. Future updates to the guidelines may address this. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Topical Janus Kinase Inhibitors

Although many topical JAK inhibitors are in development, only ruxolitinib is currently available in North America. Delgocitinib cream and/or ointment are available in other countries, albeit they may be licensed for hand eczema rather than AD.

Recommendation 8: In adolescent and adult patients with mild-moderate atopic dermatitis refractory to moisturization alone, the JTF panel suggests against adding topical ruxolitinib over continued usual care alone (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patients who place a higher value on certain larger benefits and safety profile of other topical treatments (eg, TCS 2-4, tacrolimus) and certain systemic therapies are less likely to prefer topical ruxolitinib.
2. Patients who are immunocompromised, immunosuppressed, or have risk factors for serious infection, cancer, thrombosis, or cardiovascular events (Table 6) may prefer other treatments compared with topical ruxolitinib.
3. Patients who have not responded to other topical therapies and/or those who highly value the modest benefits of topical ruxolitinib over the more certain larger benefits of other topical treatments, and ruxolitinib's uncertain association with an increased risk of cancer, thromboembolism, serious infection, and mortality, and safety profile of systemic treatments, might favor topical ruxolitinib.

Benefits and Harms: The topical treatments systematic review and NMA,[14] including 3 RCTs and more than 1400 adolescent and adult participants with mild AD (mean ~9.5% body surface area involvement and mean EASI ~8) comparing, topical ruxolitinib vs either standard care or TCS 4 (triamcinolone 0.1% cream), revealed high or moderate certainty improvements in AD severity (RD 23 more per 100 [6-41 more]), itch (34 more per 100 [20-47 more]), sleep disturbance (4 more per 100 [0-10 more]), and quality of life (35 more per 100 [25 more to 45 more]). Whether topical ruxolitinib reduces flares is highly uncertain due to imprecision and the short-term (4-8 weeks) nature of the available studies that assessed relevant interventions and controls (comparators). Topical ruxolitinib is slightly more potent in improving most patient-important AD outcomes compared to pimecrolimus (between TCS 5 and TCS 6/7)[14] (Fig 3).

Overall, adverse events within this time frame were similar between topical ruxolitinib and control groups (RD 5 fewer per 100 [12 fewer to 4 more]). The direct data were too short and did not contain enough adults (at risk) to credibly estimate the effect on death, cancer, thrombosis, or serious infections. Stroke was observed in the topical ruxolitinib group in the TRuE-AD trials, but recent data, a mix of observational and randomized data, to 40 weeks suggest favorable safety.[182] The FDA has placed a Boxed Warning label on all JAK inhibitors due to a recent study in rheumatoid arthritis and an oral pan-JAK inhibitor, tofacitinib. The Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study was a 40-month, 4362-participant study comparing tofacitinib with a TNF inhibitor in patients with rheumatoid arthritis aged 50 years or older, also taking methotrexate, and at least 1 risk factor for cardiovascular disease. Compared with TNF inhibitors, tofacitinib increased major cardiovascular adverse events (2.5% vs 3.4%; hazard ratio [HR] 1.33 [95% CI, 0.91-1.94]), cancer (2.9% vs 4.2%; HR 1.48 [1.04-2.09]), and at higher doses, venous thromboembolism (0.7% vs 2.3%), serious infections (8.2% vs 11.6%), and death from any cause (1.2% vs 2.7%). Concerns about systemic absorption with topical JAK inhibitors are sufficient to limit application of ruxolitinib to less than 20% BSA and use it in a discontinuous manner as decrease the potential for harm.[183-185] Without long-term RCTs including at-risk populations or other study designs that can robustly rule out an important increase in cancer, thrombosis, serious infection, or death (eg, using the framework used to evaluate the association with TCIs[15]), patient-important increases in serious harms with topical JAK inhibitors remain uncertain. In most mild-moderate patients with AD, the risk with a topical JAK inhibitor, however, would be predicted to be lower than that with an oral JAK inhibitor. Robust comparative long-term data are required to definitively clarify serious harms, if any, of using topical ruxolitinib.

Values and Preferences: The systematic review of values and preferences[20] and direct input from patient partners revealed that patients place a high value on safe medications and avoiding adverse

effects, to step up therapy as needed, and a strong patient-provider relationship. The panel inferred that most patients with mild-moderate AD would prefer to avoid the uncertain increase in death, cancer, thrombosis, and serious infectious, particularly when there are multiple safer treatment options with larger certain benefits and higher certainty for safety.

Contextual Factors: Any one of the serious adverse effects could lead to a significant increase in resource use. Extensive discussion and fully informing patients with mild-moderate disease before use of topical ruxolitinib are another potential resource limitation.[186] For patients who have tried other treatments or for whom they are intolerable or inaccessible, however, the time taken to discuss may be more greatly valued. Topical JAK inhibitors are likely to be available across North America, but may be limited in access to specialists with the resources and comfort with prescribing it and monitoring for its potentially rare and serious adverse effects.

Summary of Rationale: The panel inferred that most well-informed patients with mild AD would prefer to avoid the uncertain small increase in serious harms over the modest benefits of adding topical ruxolitinib compared with standard care, and in particular, when considering other treatments with higher certainty for safety.

Implementation Considerations: Consistent with the product monograph, systemic absorption, and therefore possibly serious harms, of topical ruxolitinib might be minimized when used (1) on less than 20% body surface area, (2) in nonimmunocompromized nor immunosuppressed patients, and (3) in a short-term or noncontinuous manner.

Patients and clinicians considering topical ruxolitinib should engage in a discussion of the potential benefits and harms and establish whether topical ruxolitinib or another topical or systemic therapy optimally aligns with patient values and preferences.

Similar to the recommendations for TCI or TCS, prescribing multiple agents for patients to use for different levels of AD severity or application to different body sites must take into account the potential burdens and downsides of polypharmacy. Although the panel did not yet render an official recommendation for TCS or TCI vs ruxolitinib, many clinical experts and patients will start with TCS or TCI first. Similarly, clinical experts expressed that although most patients may not prefer ruxolitinib as first-line treatment, it might be a resource to consider for those patients for whom TCS and TCI do not yield sufficient control. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Topical Antimicrobials vs No Addition of Topical Antimicrobials

Recommendation 9: In patients with uncontrolled atopic dermatitis and no serious bacterial skin infection (ie, without severe weeping, crusting, pustules, or painful skin or other signs of extensive infection or systemic illness), the JTF panel suggests against adding topical antimicrobials to standard topical treatments (conditional recommendation, very low-certainty evidence).

Conditions to consider:

1. Patients with uncontrolled AD and without serious skin infection who place a high value on avoiding polypharmacy and antimicrobial resistance will prefer to avoid adding topical antimicrobials to standard care. For severe skin infections (extent or intensity, eg, accompanied by fever or other systemic symptoms), guidance from the Infectious Disease Society of America addresses when to use systemic or topical antimicrobials.[187]
2. Patients who are immunocompromised or immunosuppressed, have a more severe (extent or intensity) infection (particularly impetigo or ecthyma[187]), a history of severe infections, severe AD, or who place a high value on avoiding potential complications of bacterial skin infections may prefer adding topical antimicrobials to standard care.

Remark: This recommendation applies to typical infected AD lesions, not the many other skin and soft tissue infections for which separate guidance from the Infectious Disease Society of America is available[187] (eg, abscesses, furuncles/carbuncles, purulent or necrotizing skin infections, erysipelas, cellulitis, animal bites, other types of skin infections).

Benefits and Harms: The topical treatments of NMA revealed that the few studies addressing the addition of topical antimicrobials in combination with TCSs or TCIs (eg, fucidin, other antibiotics or antiseptics, triclosan) compared with TCS or TCI alone in patients without severely infected AD primarily captured data only on AD severity and provided low certainty for no difference between groups.[14] These findings accord with no significant improvement across outcomes found in RCTs addressing oral antibiotics for AD (either infected[188-190] or uninfected[191-193]) and an increasing conceptual view that host-microbiome interactions in AD are more complex than the simple presence or absence of *S aureus*.[64] Although the included RCTs did adequately not report allergic contact dermatitis to the applied topical antimicrobials, this is a recognized possible complication.[194] Retrospective analysis of the 2001 to 2018 North American Contact Dermatitis Group case series of 43,722 patients with 1 or more positive allergic patch test reactions identified 6374 (15%) patients with 8787 patch test reactions to topical medications.[195] Neomycin (29%) and bacitracin (29%) made up the most common patch test reactions.

Values and Preferences: The systematic review of patient values and preferences[20] and our patient partners placed high value on safe and effective therapies. To that end, high uncertainty for any benefit at the cost of promoting antimicrobial resistance may not align with these values. Patients with AD are at risk of secondary infection and would likely value being able to have antimicrobials be effective when needed.

Contextual Factors: Although topical antimicrobials are available, their overuse contributes to antimicrobial resistance to individual patients and populations, thereby increasing resource use. Topical and systemic antimicrobial resistance caused 1.27 million deaths in 2019 alone and is now one of the top 10 threats to global health prioritized by the WHO[196] and United Nations.[197]

Summary of Rationale: The panel inferred that most well-informed patients without serious bacterial skin infection would value the high certainty for benefits with TCI and/or TCS alone over the promotion of antimicrobial resistance or other harms (including, eg, contact dermatitis) and the uncertainty for any added benefit with combining a topical antimicrobial with topical anti-inflammatory treatments such as TCI or TCS alone. The low certainty of evidence drove the conditional recommendation.

Implementation Considerations: Education regarding how the inflammatory nature of AD may hamper natural antimicrobial defenses may be helpful to frame the importance of anti-inflammatories and keeping control of AD as critical to addressing infections and preventing future ones. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Maintenance of Remission

The opening statement to the previous section, **Treating uncontrolled eczema (induction of remission)**, provides a definition and rationale for maintaining control of AD (also referred to as maintenance of remission, proactive therapy, or continued intermittent treatment). Maintaining control of AD is important to prevent flares, escalation of therapy (including systemic exposure through intense application of topical treatment and/or oral or parenteral rescue medications), and associated complications of AD and medication adverse effects.

Question 1c. Which topical treatments should be used to maintain control of AD (maintenance of remission)?

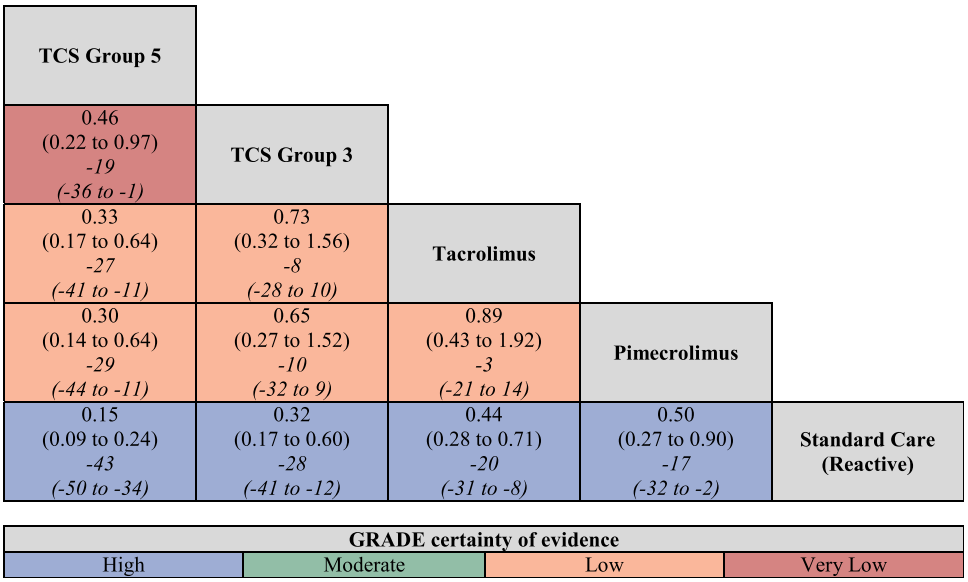

Figure 4. League table for maintenance of remission on atopic dermatitis flares.[14] The league table reveals the comparative effects of each intervention in the column compared with the intervention of the row, presented as ORs and 95% CrIs and associated *absolute risk reductions per 100 patients* (italicized). The color of each cell indicates the certainty of evidence according to GRADE. The median (interquartile range) for risk of a flare among the included studies, mostly 6 to 12 months in duration, was 63% (57% to 72%). From the linked Evidence in Allergy-JTFPP topical treatments systematic review and network meta-analysis.[14] CrIs, credible intervals; ORs, odds ratios.

As-needed vs routine intermittent use 2 to 3 times per week (proactive therapy)

Recommendation 10: In patients with atopic dermatitis and a relapsing course, the JTF panel recommends use of proactive therapy to areas that frequently flare with a topical calcineurin inhibitor or mid-potency topical corticosteroid (US classes 3-5), over applying topical treatments only in reaction to flares (strong recommendation, moderate-certainty evidence).

Benefits and Harms: The topical treatments systematic review and meta-analysis including 1964 patients across 14 RCTs, 4 to 12 months in duration, revealed that on average, proactive therapy, compared with reactive therapy, reduced the incidence of flare (69 per 100 vs 38 per 100, RD −31 [−40 to −20], relative risk: 0.55 [95% CI, 0.42-0.71]), with little to no adverse effects (24% vs 27%, RD 3 [−2 to 9]).[14] Figure 4 summarizes the less certain evidence for important differences among various TCS groups and TCIs.

Values and Preferences: The systematic review of patient values and preferences and our patient partners placed high value on safe and effective therapies and promotion of self-efficacy. By avoiding flares, proactive therapy is consistent with patient values and preferences for minimizing impact on daily life and minimizing need for intense medical therapy.

Contextual Factors: Proactive therapy is widely accessible. The included RCTs reveal that it uses less overall topical medication compared with a reactive strategy (reducing cost and potential for adverse effects), and the panel inferred it to be acceptable.

Summary of Rationale: The panel inferred that most well-informed patients with recurrent flares of AD would value the high certainty for benefits with routine intermittent use of TCI and/or TCS as proactive therapy compared with a purely reactive strategy. The certainty of evidence and important benefits with little to no harms or burdens drove the strong recommendation.

Implementation Considerations: After inducing remission, proactive therapy was best studied as application once per day on 2 consecutive days of per week (eg, weekends) for several months to maintain AD control.[14] The days that make most sense for the patient and family, however, are the best days to recommend. The overall use of once daily application of mid-potency topical medications (Recommendation 6) may help facilitate proactive therapy. The corresponding Good Practice Statement's recommendation for education and handouts, such as an action plan, continue to apply for optimally keeping control of AD. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Mechanisms of Action of Topical Treatments

Topical therapies can have both local and systemic effects depending on the molecule and systemic absorption. Topical corticosteroids are absorbed into cell membranes, including dermal and epidermal cells, and leukocytes, and bind to glucocorticoid receptor (GR) and lead to increased production of lipocortin. Lipocortin inhibits phospholipase A2, which inhibits prostanoids and leukotrienes. GR also up-regulates anti-inflammatory pathways and decreases stability of mRNA coding for molecules such as collagenase, elastase, chemokines, and cytokines.

The TCIs bind to FK506-binding protein in the cells. The drug suppresses calcineurin activity leading to decreased expression of both T_H1 and T_H2 cytokines and interferon-gamma and tumor necrosis factor-alpha. However, TCI are larger molecules, so they have less systemic absorption.

Topical JAK inhibitors (sometimes abbreviated as JAKibs or JAKinibs) preferentially inhibit one, or many, JAK molecules depending on the specificity of the drug. Delgocitinib, for instance, is a pan-JAK inhibitor that blocks JAKs 1 to 3 and TYK2. Inhibition of the JAK pathway leads to reduced activation of STAT proteins which can lead to broad reduction of cytokines and chemokines. The JAK-STAT pathway also controls cellular division and death. JAK inhibitors are small molecules, so they have greater potential for systemic absorption and adverse events.

PDE4 (phosphodiesterase-4) inhibitors reduce the enzyme activity of PDE4. PDE4 degrades cyclic adenosine monophosphate (cAMP). cAMP plays a role in cell regulation and can affect both pro-inflammatory and anti-inflammatory cytokine synthesis, activation of T cells, and antigen presentation.

Bleach Baths

Question 2. Should bleach baths be used for atopic dermatitis?

What is the best evidence regarding the benefits and harms of bleach baths to treat AD, and in whom should they be used?

Recommendation 11: In patients with moderate-severe atopic dermatitis, the JTF panel suggests, in addition to topical therapy, dilute bleach baths over usual (no dilute bleach-based) baths (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Whether the dilute bleach bath routine will fit into the patient's routine.
2. The provision of clear and written instructions specific to dilute bleach baths may favor using bleach baths over not.
3. The extent of a patient's open skin (cracks, fissures, excoriations) may lead to it being less tolerable by some patients, whereas other patients find it relieving.

Benefits and Harms: The linked systematic review and meta-analysis synthesizing 10 RCTs[16] revealed that the probability to improve AD severity by 50% with adjunctive dilute bleach baths was 32% vs 22% in the control group (moderate certainty). Similar effects were found in studies enrolling participants with or without a history of skin infections. No differences in effect by age were found. Patients using dilute bleach baths were likely to see effects in AD severity within 4 weeks of treatment. Dilute bleach baths compared with usual baths may lead to little to no difference of adverse events, with mild events consisting of dry skin and irritation (low certainty). Changes in other patient-important outcomes (eg, itch, patient-reported disease severity, sleep quality, AD-related quality of life, and risk of AD flares) were uncertain.

Values and Preferences: The linked systematic review of patient and caregiver values,[20] along with direct patient and caregiver input, addressing their perspectives on bleach baths revealed that patients valued a noncorticosteroid-based adjunctive therapy and that they found the intervention acceptable, feasible, and widely available. Particularly when AD severity was moderate-severe, most well-informed patients would likely place a high value on a small but important reduction in disease severity and the time that it takes to achieve such improvement. The values and preferences, however, are likely to vary compared with patients with less severe disease. For example, a patient with a high disease severity such as an EASI (scale of 0-72 with higher being worse) of 40 might observe a modest improvement by 8.8 points, whereas those presenting with low disease activity, such as an EASI of 10, may experience little to no improvement (improve by 2.2 points). The panel inferred that patients, regardless of severity, are likely to value the more certain potential benefits of adjunctive dilute bleach baths compared with its less certain small harms.

Contextual Factors: The low cost of bleach and a measuring cup are unlikely to have an important impact on the costs for most patients. Dilute bleach baths might improve equity in populations in remote areas that have access to bleach and baths but are sufficiently remote to make medical visits difficult. Though bleach baths can be associated with an odor and a routine to become familiar with, the panel inferred this treatment to be acceptable to most well-informed patients. Dilute bleach baths are as feasible as usual baths without bleach. The eAppendix presents practical information about how to use dilute bleach bathing, including when no bath is available.

Summary of Rationale: The panel inferred that patients would value the moderate certainty for a 10% higher chance of halving the severity of their AD and considering bleach's wide availability and likely acceptability. The panel determined that, overall, patients would find dilute bleach baths worthwhile given the minimal downsides. The low certainty for benefits in other important patient-reported outcomes and potential harms, however, contributed to the conditional recommendation. Specifically, in patients with moderate-severe disease, dilute bleach baths can be suggested if it is minimally disruptive to the patient's routine, used as an adjunct to otherwise good skin care, if clear written instructions can be provided, and after consideration of the overall extent of open skin (see practical issues).

Implementation Considerations: The panel emphasized that dilute bleach baths should be adjunctive to standard AD skin care (moisturizing, topical medication use, action plans for flare management) and that considering adjunctive dilute bleach baths should not detract from fundamental skin care routines (see Good Practice Statement). The eAppendix and online resources present additional guidance.

Recommendation 12: In patients with mild atopic dermatitis, the JTF panel suggests against adding dilute bleach baths to topical therapy (no dilute-bleach based) baths (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patient values and preferences regarding the small magnitude of potential benefit vs the burdens and potential harms, in addition to the factors described previously.

Benefits and Harms: The estimated treatment effect of dilute bleach baths for milder AD (eg, EASI of 10) was, on average, small (−2.2 points in comparison to a minimally important difference of 6.6). All other findings were similar to those described in Recommendation 11.

Values and Preferences: The guideline panel inferred that most well-informed patients with mild AD are likely to place a high value on maintaining a simple treatment routine that is minimally disruptive to their daily life. The panel inferred that most, but not all, patients with low disease activity would place a low value on a trivial improvement in AD in comparison to the burden and practical implications of dilute bleach baths.

Contextual Factors: Similar to those described in Recommendation 11.

Summary of Rationale: As described previously, the magnitude of benefit in AD severity is likely to be smaller in those with less severe disease. The panel viewed that most fully informed patients are likely to value avoidance of the burdens of bleach baths and their uncertain harms over likely a small, possibly unimportant, benefit in AD severity. The panel, however, acknowledged that there may be substantial variability in values and preferences such that a number of patients might opt for adjunctive dilute bleach baths even if their disease activity is mild.

Mechanism of Action of Dilute Bleach Baths

The initial hypothesis for the mechanism of action of dilute bleach baths in AD was that it would have a direct antibacterial activity, in particular against the overabundance of *S aureus*.[64,198] However, subsequent investigations have revealed that at the concentrations used clinically, the sodium hypochlorite (active ingredient in the dilute bleach bath) in vitro is not actually antimicrobial against *S aureus*.[199] Other studies have instead suggested anti-inflammatory, antipruritic, and barrier-restoring properties of dilute bleach baths, any or all of which may be playing a role in improving clinical outcome in selected patients with AD.

Elimination Diets (With or Without Skin Testing)

Question 3. Should elimination diets be used for atopic dermatitis?

Recommendation 13: In patients with atopic dermatitis, the JTF panel suggests against the use of elimination diets compared with an unrestricted diet (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Young age of patient (eg, infant) and other risk factors for developing IgE-mediated food allergy would favor against pursuing an elimination diet.
2. Risk for malnutrition would favor against pursuing an elimination diet.

Remark: These recommendations apply to patients regardless of whether or not they are already using topical treatments or moisturizers.

Benefits and Harms: Although observational studies and patients may report the potential for food ingestion to provoke eczematous reactions in patients with AD, whether a food may be associated with provoking eczematous dermatitis is a distinct question from whether avoiding foods (dietary elimination) will improve AD.[17] The systematic review and meta-analysis identified 10 RCTs (599 participants) addressing benefits and harms of dietary elimination for AD.[17] Compared with no dietary elimination, low-certainty evidence revealed that dietary elimination may slightly improve AD severity (50% with vs 41% without dietary elimination improved by a minimally important difference, RD of 9% [95% CI, 0-17]), pruritus (itch score [range, 0-3] MD, −0.21 [95% CI, −0.57 to 0.15]), and sleeplessness (sleeplessness score [range, 0-3] MD, −0.47 [95% CI, −0.80 to −0.13]). Bayesian sensitivity analyses revealed that most individuals pursuing a diet elimination strategy would most likely experience little to no benefit. A testing directed strategy was no more efficacious than empirical elimination.

Insufficient direct evidence was reported regarding harms of elimination diets among the included studies. However, indirect evidence in infants (89% with severe AD) evaluating peanut elimination vs ingestion until age 5 years revealed an RR of 5.03 (95% CI, 2.64-9.56) and RD of 14% for the development of peanut allergy and an RR of 4.33 (95% CI, 1.25-15.06) and RD of 3% for anaphylaxis. AD severity and time spent avoiding foods are also reported risk factors for the development of peanut allergy (OR, 1.19; 95% CI, 1.06-1.34 per 5 points; OR, 1.3; 95% CI, 1.04-1.68 per month[200]). The evidence regarding malnutrition as an adverse outcome from dietary elimination, being primarily informed by case reports and uncontrolled case series, is very uncertain.

Values and Preferences: The linked systematic review[20] along with direct patient and caregiver input on their perspectives on dietary elimination revealed that many patients with AD will consider a diet therapy; value nonpharmacologic therapies; highly value safe interventions; and place a high value on avoiding acquiring another chronic condition such as food allergy.

Between both the uncertain benefits and uncertain harms,[17] the panel inferred that most well-informed patients would place a higher value on avoiding potentially large harms. This was particularly the case in infants and children where risk for developing food allergy is thought to be greater. All ages, however, were thought to be at risk of malnutrition and the burdens to patients and their caregivers associated with following a strict dietary elimination strategy.

Contextual Factors: Strictly following a food elimination diet is associated with higher food-related costs. The feasibility of avoiding foods and accessibility to suspected-allergen free foods may vary.

Summary of Rationale: The panel inferred that most well-informed patients would value avoiding uncertain harms (eg, 14% higher chance of developing a potentially lifelong food allergy) and burdens compared with uncertain small benefits in AD control (9% higher chance of small, potentially unimportant, improvement), particularly in infants and children. The low certainty for benefits and harms, close balance of their magnitudes of effect, and anticipated variability in values and preferences, particularly with age, contributed to the conditional recommendation.

Implementation Considerations: Although the systematic review and meta-analysis did not reveal any difference between test-guided and non–test-guided elimination for AD, the available data suggest against screening using allergy testing for the purposes of food elimination.[17] This practice is associated with a high risk of false-positive testing that could promote harm through food removal in a sensitized but unexposed infant and, therefore, increase the risk of developing IgE-mediated food allergy.[17,200] This effect may be magnified in very young infants where such practices are currently frequently used. If patients are nonetheless going to pursue dietary elimination, potential strategies to mitigate harm include providing information on what managing a food allergy entails and scheduling close follow-up (eg, within 4 weeks), especially in infants and young children to mitigate the risk of promoting IgE-mediated food allergy or malnutrition. N-of-1 trials (eg, in individual patients, 3 cycles of 2-week crossover trials alternating between elimination vs inclusion) with jointly prespecified measures (eg, EASI and POEM) and end points may be a more objective way to document response with close follow-up and preventing prolonged elimination of foods.[201,202] The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Mechanism of Action of Dietary Elimination

The slight effect of dietary elimination on AD severity suggests that through ingestion or contact, food may be a minor contributor to causing or perpetuating AD. The mechanism(s) may be allergic or nonallergic. Some data suggest higher T cell proliferative responses (of both T_H1 and T_H2 cells) to triggering foods and possibly trafficking of antigen-specific T cells to lesional skin in food allergen-responsive AD.[203-205] Although elevated food allergen-specific IgE levels are frequently encountered in patients with AD, total IgE levels are often globally increased with nonspecific expansion of particular food-specific IgE. Furthermore, non–IgE-reactive T cell epitope-containing fragments in sensitized patients may elicit eczematous skin inflammation.[206] Allergen-specific IgE may also allow for greater antigen presentation by dendritic cells, which in turn facilitates increased T cell activation.[207] Further research is needed to clarify the connection, if any, of food-specific innate and adaptive immunities to AD.

Allergen Immunotherapy (Subcutaneous and Sublingual)

Question 4. Should allergen immunotherapy be used for atopic dermatitis?

What is the best evidence regarding the benefits and harms of allergen immunotherapy (AIT) to treat AD, and in whom should it be used?

Recommendation 14: In patients with moderate-severe atopic dermatitis refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel suggests adding allergen immunotherapy to standard topical treatment over not adding (conditional recommendation, moderate-certainty evidence).

Conditions to consider:

1. Allergic comorbidities that will likely be responsive to immunotherapy (eg, allergic rhinitis, or asthma with relevant sensitization) may lead to benefits for multiple diseases and therefore favor AIT.
2. Values and preferences regarding SCIT vs SLIT (eg, convenience, age, travel plans).
3. The plausibility of allergen sensitization to reflect allergy. For example, a patient sensitized to horse dander with no further plausible exposure to horse dander will unlikely benefit from AIT to horse. In contrast, a patient with dust mite sensitization and dust mite exposure might benefit from AIT to dust mite.

Benefits and Harms: The linked systematic review of 23 RCTs (11 SCIT and 12 SLIT) included 1957 adult and pediatric patients (median of study mean ages, 19 years; range of means, 4-34 years).[18] Most of the studies desensitized patients to HDMs (*D pteronyssinus* and/or *D farinae*), whereas 4 included other inhaled allergens (eg, pollens). The studies treated patients with AIT typically for 12 (range 3-36) months. Patients were mostly on standard topical therapy including TCSs and moisturizers with AIT added on. Most of the studies included polysensitized patients in addition to HDM sensitization.

Based on a combination of clinician-reported AD severity (eg, SCORAD), AIT likely improved AD severity by 50% or more from baseline compared with no AIT (40% vs 26%), with similar estimates of effect for SCIT and SLIT. Crude estimates of median time to effect were 5 (range 1-12) months. Eight studies also revealed improvement in health-related quality of life, based on a 4-point or more improvement in dermatology life quality index (DLQI): AIT as compared with no AIT (56% vs 39%).

The main adverse effects were similar to AIT for allergic rhinitis and asthma, that is, local injection site reaction for SCIT (66% of individuals) and oropharyngeal itching for SLIT (13% of individuals). Systemic reactions or those severe enough to cause discontinuation occurred in approximately 10% of those receiving SCIT and were rare with SLIT (0.14% systemic reaction; 1.2% discontinue).

Values and Preferences: The linked systematic review[20] along with direct patient and caregiver input revealed that patients with AD value nonpharmacologic therapies, safe interventions, stepping-up therapy based on severity, and a strong patient-provider relationship. They also value odorless and nonvisible treatments and those that do not interfere with daily activities.

The panel inferred that most well-informed patients would value the moderate certainty for net benefit with AIT and that there would be variability in patient values and preferences regarding the burden associated with SCIT (multiple clinician visits for administration; often starting as weekly) and SLIT (daily self-administered medication) and time to effect (crude estimate of months as described previously).

Contextual Factors: Accessibility to specialists with expertise in AIT is required to initiate the treatment. To receive SCIT, a clinician and facility capable of treating systemic allergic reactions including anaphylaxis are required.

Summary of Rationale: The panel inferred that most well-informed patients would value moderate-certainty benefits over little to no harms with SLIT. With SCIT, the balance between benefits and harms is closer. With both interventions, the burdens and anticipated variability in values and preferences, particularly with age, severity of disease, and allergic comorbidities, contributed to the conditional recommendation.

Implementation Considerations: The available SLIT studies addressed SLIT drops, whereas most allergists in the United States may be most familiar with SLIT tablets. SLIT tablets are FDA-approved for dust mites, grass, and ragweed for allergic rhinitis; dust mite for 12 years to 65 years of age and grass and ragweed for 5 years to 65 years of age. Separate AIT practice parameters state that there is no specific upper or lower age limit for initiating AIT if indications are present and after considering the absence of significant comorbid conditions and the patients' ability to complete AIT.[208] Registries or surveillance studies, such as the AAAAI/ACAAI AIT surveillance study, may help address research gaps.[209-214] The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Recommendation 15: In patients with mild atopic dermatitis, the JTF panel suggests against adding allergen immunotherapy to standard topical treatment (conditional recommendation, moderate-certainty evidence).

Conditions to consider:

1. Patients with allergic comorbidities with relevant sensitization that will likely be responsive to AIT (eg, allergic rhinitis, asthma) may be more likely to pursue this treatment even if their AD is mild if it means that multiple conditions will improve. In contrast, most individuals with mild AD and no other allergic comorbidities will likely not pursue this treatment.
2. Values and preferences regarding SCIT vs SLIT (eg, convenience, age, travel plans).

Benefits and Harms: Although the harms are thought to remain the same as in the moderate-severe population, the magnitude of benefit is likely smaller in those with mild disease, and hence, the panel inferred that the net benefit may be small.

Values and Preferences: The panel inferred that most well-informed patients would not value a small net benefit with AIT for AD. They recognized, however, that patients with AD tend to have other allergic comorbidities, and the treatment may benefit more than one disease. In these cases, patients might value treating multiple diseases with an expectation of an important improvement in overall symptom burden across multiple allergic diseases.

Contextual Factors: Similar to those presented in Recommendation 14.

Summary of Rationale: The panel inferred that most well-informed patients would value avoiding the inconvenience of SCIT or SLIT over the moderate-certainty for small benefits. The anticipated variability in values and preferences, particularly with age and allergic comorbidities, contributed to the conditional recommendation.

Mechanism of Action of Allergen Immunotherapy

Allergens, such as HDM, may drive innate and adaptive inflammatory processes through specific cellular and humoral mechanisms[215,216] beyond contributing to epidermal barrier disruption through their allergen-intrinsic enzymatic activity[217-219] and direct innate cell activation.[220,221] These mechanisms could lead to the elaboration of multiple cytokines including IL-4 and IL-13 from T cells and local production of TSLP, IL-25, IL-33, and GM-CSF[62,222,223] by multiple cellular sources that promote skin inflammation and itch. Conversely, AIT's multiple anti-inflammatory, immunomodulatory, and protolerogenic mechanisms, including induction of IL-10 production by innate cells, epithelial repair, and modulation of the JAK-STAT pathway,[224-227] might explain the clinical benefits observed in the meta-analysis. Additional research is needed to better understand the mechanisms by which allergens and AIT affect AD and might interact with the other factors that drive disease.

Systemic Treatments

Question 5. Which systemic treatments (eg, biologics, small molecule immunosuppressants, phototherapy) should clinicians prescribe to treat atopic dermatitis?

There are multiple options for systemic treatment of AD refractory to, at least, topical therapy. Such patients will often have moderate-severe disease. These include biologics (mostly monoclonal antibodies that target IL-4 and IL-13 cytokine signaling pathways, or IL-13 signaling alone; see **Mechanisms of action of systemic treatments** section for more details), small molecules (mostly immunosuppressants), and UV light therapy (phototherapy).

Dupilumab

Recommendation 16: In patients 6 months of age or older with moderate-severe AD refractory, intolerant, or unable to use mid-potency or greater topical treatment, the JTF panel recommends adding dupilumab over continued standard topical treatment without dupilumab (strong recommendation, high-certainty evidence).

Benefits and Harms: The linked systematic review and NMA of 149 RCTs evluating 75 interventions in 28,686 patients revealed that compared with continued standard topical treatment alone, adding dupilumab led to large improvements in multiple patient-important outcomes (Fig 5 presents an abbreviated summary of findings from systemic NMA) including AD severity, judged either by patients or clinicians, itch, sleep disturbance, AD-related quality of life, without an increase in serious adverse events or adverse events leading to discontinuation. Conjunctivitis, however, was higher (6% [95% CrI, 4%-9%] with dupilumab vs 2% with placebo). Safety data included studies lasting 52 weeks in duration, and even longer-term (multi-

	Atopic Dermatitis Severity EASI (0–72)	Patient-Reported AD Severity POEM (0–28)	Itch NRS (0–10)	Sleep Disturbance NRS (0–10)	Eczema-Related Quality of Life DLQI (0–30)	Atopic Dermatitis Flares	Any Adverse Event	Serious Adverse Event
	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	MD (95%CrI)	RD (95%CrI)	RD (95%CrI)	RD (95%CrI)
Baseline	29.00	20.87	7.10	5.30	14.74	139 per 1000	592 per 1000	22 per 1000
Cytostatics and Immunophilin Agents								
Azathioprine	-4.95 (-9.70 to -0.22)		-1.41 (-2.75 to -0.06)	-1.30 (-2.88 to 0.28)	-3.05 (-6.30 to 0.19)	-108 (-139 to 644)	193 (-541 to 404)	5 (-21 to 852)
Cyclosporine 4–5mg/kg (High Dose)	-13.38 (-17.01 to -9.83)		-2.05 (-2.79 to -1.33)	-1.45 (-2.37 to -0.58)	-8.34 (-12.54 to -4.11)		215 (22 to 324)	0 (-18 to 87)
Cyclosporine 2–3mg/kg (Low Dose)	-6.73 (-10.96 to -2.52)		-0.96 (-1.81 to -0.14)	-0.12 (-0.97 to 0.68)	-5.93 (-9.81 to -2.07)	0 (-136 to 757)	138 (-106 to 294)	35 (-18 to 516)
Methotrexate	-6.88 (-11.93 to -1.88)		-1.30 (-3.40 to 0.79)	-0.30 (-2.73 to 2.13)	-3.67 (-7.40 to 0.03)	-86 (-138 to 672)	177 (-154 to 343)	7 (-21 to 566)
Mycophenolate	-8.71 (-16.69 to -0.74)							
Monoclonal Antibodies								
Astegolimab	4.47 (-5.17 to 14.10)		0.66 (-1.20 to 2.54)			-64 (-122 to 133)	-169 (-377 to 71)	37 (-19 to 591)
Benralizumab	0.13 (-10.79 to 10.99)							
Dupilumab (Standard Dose)	-10.72 (-12.30 to -9.19)	-7.05 (-7.64 to -6.50)	-2.14 (-2.38 to -1.90)	-1.84 (-2.26 to -1.42)	-4.56 (-5.18 to -3.98)	-74 (-83 to -64)	-20 (-50 to 10)*	-11 (-14 to -7)
Fezakinumab	-4.98 (-13.97 to 4.02)						-52 (-312 to 188)	34 (-19 to 539)
Itepekimab	-3.82 (-11.33 to 3.68)		-1.30 (-2.74 to 0.13)			-55 (-105 to 57)		-13 (-21 to 55)
Lebrikizumab (Standard Dose)	-9.10 (-12.36 to -5.84)	-6.10 (-9.40 to -2.76)	-1.77 (-2.32 to -1.24)	-1.59 (-2.09 to -1.08)	-3.92 (-5.55 to -2.31)	-73 (-124 to 108)	70 (-48 to 171)*	-15 (-20 to 12)
Mepolizumab	-3.48 (-9.89 to 2.93)	-4.21 (-7.30 to -1.13)	-1.30 (-3.03 to 0.41)				-507 (-582 to -124)	-2 (-21 to 489)
Nemolizumab	-3.40 (-7.36 to 0.52)	-4.77 (-7.24 to -2.35)	-2.16 (-2.88 to -1.44)	-1.78 (-2.41 to -1.16)	-1.95 (-3.40 to -0.49)	3 (-42 to 66)	38 (-52 to 121)	4 (-13 to 51)
Omalizumab	0.17 (-6.81 to 7.23)	-0.51 (-3.59 to 2.51)			-4.01 (-6.76 to -1.22)	-20 (-104 to 194)	80 (-317 to 325)	0 (-15 to 45)
Tezepelumab	-2.13 (-6.98 to 2.68)		-0.57 (-1.95 to 0.81)				-66 (-258 to 118)	-8 (-18 to 32)
Tralokinumab (Standard Dose)	-6.45 (-8.67 to -4.27)	-4.47 (-5.37 to -3.58)	-1.08 (-1.51 to -0.65)	-0.93 (-1.36 to -0.49)	-2.36 (-3.21 to -1.51)	-57 (-72 to -40)	-1 (-43 to 40)*	-8 (-13 to 1)
Ustekinumab	1.58 (-5.01 to 8.27)		0.03 (-1.69 to 1.76)		-0.60 (-2.82 to 1.67)	-87 (-121 to 0)	-102 (-337 to 137)	-5 (-21 to 191)
Oral JAK Inhibitors								
Abrocitinib 200mg (High Dose)	-9.44 (-11.90 to -6.98)	-7.38 (-8.23 to -6.51)	-2.22 (-2.62 to -1.83)	-1.74 (-2.17 to -1.29)	-4.56 (-5.39 to -3.71)	-121 (-127 to -114)	85 (45 to 122)†	0 (-10 to 18)‡
Abrocitinib 100mg (Low Dose)	-6.89 (-9.49 to -4.28)	-4.69 (-5.62 to -3.74)	-1.40 (-1.82 to -0.99)	-0.96 (-1.40 to -0.51)	-2.81 (-3.73 to -1.92)	-93 (-105 to -78)	5 (-42 to 51)†	-1 (-11 to 16)‡
Baricitinib 2–4mg (High Dose)	-5.99 (-8.78 to -3.22)	-4.51 (-5.61 to -3.39)	-1.24 (-1.71 to -0.77)	-1.30 (-1.80 to -0.81)	-2.80 (-3.78 to -1.81)	-69 (-114 to 40)	60 (18 to 99)†	-6 (-13 to 6)‡
Baricitinib 1mg (Low Dose)	-3.47 (-6.81 to -0.12)	-2.21 (-3.60 to -0.80)	-0.69 (-1.27 to -0.11)	-0.91 (-1.52 to -0.29)	-1.48 (-2.72 to -0.23)	-34 (-110 to 176)	19 (-36 to 72)†	8 (-6 to 36)‡
Upadacitinib 30mg (High Dose)	-13.99 (-16.62 to -11.37)	-8.26 (-9.41 to -7.20)	-2.91 (-3.35 to -2.49)		-9.76 (-11.23 to -8.28)	-125 (-132 to -111)	108 (72 to 141)†	-4 (-11 to 7)‡
Upadacitinib 15mg (Low Dose)	-11.43 (-14.25 to -8.64)	-6.54 (-7.64 to -5.45)	-1.90 (-2.35 to -1.45)		-8.36 (-9.83 to -6.89)	-115 (-124 to -101)	55 (14 to 95)†	-5 (-12 to 7)‡
UV Light Therapy								
Narrow-Band UVB	-5.45 (-11.68 to 0.77)			-2.50 (-4.06 to -0.93)				
UVA/UVB Therapy	1.90 (-3.42 to 7.07)			-1.60 (-3.25 to 0.04)	-5.60 (-10.19 to -0.96)		-140 (-531 to 321)	36 (-21 to 874)
Other								
Oral Corticosteroid	-4.28 (-14.70 to 6.08)	-3.76 (-10.72 to 3.11)	-0.97 (-2.20 to 0.24)	-0.58 (-1.76 to 0.56)	-4.80 (-9.36 to -0.27)	133 (-134 to 824)		190 (-18 to 930)
Montelukast	-3.45 (-6.50 to -0.44)		0.71 (-0.54 to 1.95)	0.61 (-0.71 to 1.92)			-8 (-515 to 368)	42 (-19 to 614)

High to moderate certainty evidence	Low to very low certainty evidence
Among the most effective	Possibly among the most effective
Among the intermediate (superior) effective	Possibly among the intermediate (superior) effective
Among the intermediate (inferior) effective	Possibly among the intermediate (inferior) effective
Not clearly different from placebo	Possibly not clearly different from placebo
Among the intermediate harmful	Possibly among the intermediate harmful
Among the most harmful	Possibly among the most harmful

Figure 5. Summary of comparative effects of systemic treatments on patient-important outcomes for atopic dermatitis (eczema). The certainty of the evidence was rated by the GRADE criteria. We categorized the interventions according to a minimally contextualized framework with a target of certainty of a non-zero effect. The effectiveness categories depict the magnitude of the treatment effect, whereas the certainty of the evidence shows whether the effect is trustworthy or not. Detailed categorizations of all 75 interventions are presented in the linked systematic review manuscript.[19] *Although dupilumab, lebrikizumab, and tralokinumab did not demonstrate an increase in the frequency of any adverse event, they increased the frequency of conjunctivitis compared with standard care. †Abrocitinib, baricitinib, and upadacitinib also increased the frequency of viral skin infections specifically, such as herpes zoster. ‡The long-term ORAL study found that tofacitinib, an oral JAK inhibitor, was associated with increased major cardiovascular events, cancer, venous thromboembolism, serious infections, and death from any cause. From linked Evidence in Allergy-AAAAI/ACAAI JTFPP network meta-analysis.[19] Data updated to October 19, 2023 produced similar findings. CrI, credible interval; MD, mean difference; RD, risk difference.

year) safety data have been reported to further support this recommendation.[228,229]

Dupilumab is approved for several conditions that are often comorbid with AD. Benefits could therefore also include treatment of associated conditions such as prurigo nodularis, eosinophilic esophagitis, asthma, and chronic sinusitis with nasal polyps.[230,231]

Values and Preferences: The linked systematic review[20] along with direct patient and caregiver input revealed that patients with AD value stepping-up therapy based on severity, safe medications, relief, and normalization of daily activities, and a strong patient-provider relationship, despite the need for injections and potential fear of needles. They also value odorless and nonvisible treatments and those that do not interfere with daily activities. Patients/caregivers may also value having one systemic therapy treat multiple comorbidities.

Contextual Factors: Dupilumab is generally available and acceptable in North America. Taking a biologic medication, however, requires additional coordination in terms of obtaining the medication, insurance paperwork, keeping the drug temperature-controlled, and administering it. Biologics are often self-administered. If they are administered by a health care professional (eg, at a physician's office or at an injection clinic), however, then there may be added time and cost considerations.

Summary of Rationale: The panel inferred that most well-informed patients would place a high value on the large and high-certainty

benefits of dupilumab, with moderate-certainty long-term safety, over the minor increase in inconvenience and added coordination needs with receiving or self-injecting the medication.

Implementation Considerations: The precise dosing and frequency of administration depend on age and weight. Though dupilumab is effective as monotherapy, the JTF panel recommends it as combination therapy with topical treatment. Dupilumab can be combined with, as indicated, AIT and dilute bleach baths. Implicit in this recommendation is that a patient need not to trial cyclosporine, other small molecule immunosuppressants, or UV light (or AIT or dilute bleach baths) before being eligible for dupilumab—this is particularly important to address inequity in access to optimal treatments for patients, or to treat multiple conditions with a single medication. The optimal definition or period before designating a patient's AD as refractory to mid- to high-potency topical treatment is unclear. The available RCTs systematically reviewed (topical and systemic NMAs)[14,19] and AD experts typically expect response to mid- or high-potency topical therapy within 2 to 6 weeks.

Conjunctivitis can be an adverse effect of dupilumab (systemic NMA).[19] Patients may experience dry, red, itchy eyes, tearing and foreign body sensation, and eczematous rashes around their eyes. Prior history of conjunctivitis and more severe AD before start of dupilumab may be risk factors for conjunctivitis with dupilumab treatment.[232] Some protocols suggest a baseline eye examination by an ophthalmologist and the use of lubricant eye drops (artificial tears) twice daily when dupilumab is initiated, but practice varies. Mild conjunctivitis may respond to warm compresses, lubricant eye drops, and if there is concomitant allergen exposure, antihistamine eye drops. Patients with symptoms of severe ocular disease, such as blurred vision, decrease in visual acuity, purulent eye discharge, photophobia, or eye pain, should be urgently or emergently evaluated by ophthalmology. Treatment with opthalmic topical corticosteroids or other immunomodulatory (tacrolimus, cyclosporine, lifitegrast) eye drops may be needed to treat the conjunctivitis and prevent its potential complications. Treatment of any eczema around the eyes with topical tacrolimus ointment or pimecrolimus cream may help with reducing ocular itching and rubbing.

Patients of any age, especially children, may fear injections or find them to be painful. When there is a plan for dealing with injections, there may be less fear and pain. Providing developmentally appropriate explanations of how the treatment will help and what to expect can increase their sense of control. Potential strategies to reduce fear and pain may include distraction (eg, listening to music), creating a routine, relaxed breathing (or blowing bubbles for young children), icing the area to numb the skin, using a topical anesthetic, or using a ShotBlocker or Buzzy device (cold/vibration) to reduce pain signals. Planning an enjoyable activity after the injection and talking about what went well can also reduce stress. If fear of needles leads to significant avoidance/delaying of injections, consider referral to a mental health professional for exposure-based therapy.[233] Some patient partners shared that they preferred the medication to come to room temperature before injection, whereas others did not mind using soon after removal from the refrigerator. Likewise, some remarked that they found the autoinjector less painful compared with the prefilled syringe. The eAppendix provides additional practical information and implementation considerations, including navigating vaccines/immunizations, in 1-2 page handouts.

Remark: The panel has issued a strong recommendation for dupilumab or tralokinumab and a conditional recommendation for AIT. Individuals can be on both immunotherapy and a biologic treatment simultaneously. Although the panel has not rendered an official recommendation regarding a biologic vs immunotherapy, if patients pursue only one or the other treatment, many patients might prefer dupilumab or tralokinumab over AIT if they value its (1) larger treatment effects and higher certainty across multiple patient-important outcomes, (2) initially less frequent injections (common SCIT schedules start with weekly injections), and (3) ability to self-inject a biologic if desired. If injections wish to be completely avoided, however, SLIT or other oral systemic options may be desirable. Clinicians facing such situations seeking optimal AD management will engage in shared decision-making with patients and families to ensure that treatment choices reflect patient values and preferences.

Benefits and Harms: The linked systematic review and NMA revealed that compared with continued standard care alone, adding tralokinumab led to improvements in multiple patient-important outcomes (Fig 5 presents an abbreviated summary of findings from the systemic NMA[19]), including AD severity, judged either by patients or clinicians, itch, sleep disturbance, AD-related quality of life, without an increase in serious adverse events or adverse events leading to discontinuation. Compared with dupilumab, tralokinumab was one category lower across multiple patient-important outcomes. Conjunctivitis, however, was similar between both tralokinumab and dupilumab. The safety data to date are reassuring. No randomized trials of tralokinumab address infants or young children with AD.

Values and Preferences: The linked systematic review[20] along with direct patient and caregiver input revealed that patients with AD value stepping-up therapy based on severity, safe medications, relief and normalization of daily activities, despite the need for injections and potential fear of needles, and a strong patient-provider relationship. They also value odorless and nonvisible treatments and those that do not interfere with daily activities.

Contextual Factors: Taking a biologic medication requires additional coordination in terms of obtaining the medication, keeping it temperature controlled, and administering it. Biologics are often self-administered or administered by a caregiver, but if they are administered by a health care professional (eg, at a physician's office or at an injection clinic), then there may be added time, travel, and cost considerations.

Summary of Rationale: The panel inferred that most well-informed patients would place a high value on the large and high-certainty benefits of tralokinumab, with moderate-certainty long-term safety, over the minor increase in harms, and inconvenience and added coordination needs with receiving or self-injecting the medication.

Implementation Considerations: Although the panel provides strong recommendations for dupilumab or tralokinumab, available evidence does not address combination therapy, and as such, the panel recommends using either agent, based on contextual factors, rather than both agents together. The panel did not yet issue a formal recommendation for one agent over the other. The evidence for benefits, however, provides stronger support for dupilumab compared with agents targeting solely IL-13, such as tralokinumab or lebrikizumab. See the practical issues (eAppendix) and Recommendation 16 addressing dupilumab regarding implicit aspects of the recommendation, conjunctivitis, and injections.

Tralokinumab

Recommendation 17: In patients 12 years of age or older with moderate-severe AD refractory, intolerant, or unable to use mid-potency topical treatment, the JTF panel recommends adding tralokinumab over continued topical treatment without tralokinumab (strong recommendation, high-certainty evidence).

Oral JAK Inhibitors (Abrocitinib, Baricitinib, Upadacitinib)

There are multiple oral JAK inhibitors currently available and additional ones in development. Most oral JAK inhibitors are licensed first to address autoimmune conditions, such as rheumatoid arthritis or inflammatory bowel disease, or in the case of baricitinib, severe or

critical COVID-19 and severe alopecia areata. See the mechanism of action section regarding details of their selectivity.

Recommendation 18: In adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously, the panel suggests replacing the systemic treatment with one of the following oral JAK inhibitors (alphabetical order: abrocitinib 100-200 mg [age 12 years or above], baricitinib 2-4 mg [age 18 years or above], upadacitinib 15-30 mg [age 12 years or above]) over not using one of these JAK inhibitors (conditional recommendation, low-certainty evidence). See Recommendation 19 regarding baricitinib 1 mg dose.

Conditions to consider:

1. Oral JAK inhibitors are contraindicated in pregnancy and breastfeeding: per data summarized in the drug monographs, oral JAK inhibitors increased fetal malformations (teratogenic) or fetal toxicity in drug-development animal safety studies. Baricitinib decreased male and female fertility in animals. Abrocitinib, baricitinib, and upadacitinib are excreted into milk in lactating animals (eg, upadacitinib exposure was approximately 30-fold greater in milk than in maternal plasma, of which approximately 97% of drug-related material in milk was parent drug). Direct human data addressing safety in conception, pregnancy, and breastfeeding are sparse and uncertain.
2. Risk factors for adverse outcomes, including age or history of or other strong risk factors for cancer, serious infection, venous thrombosis, or cardiovascular disease, favor against JAK inhibitor use in these populations.
3. Approved age differs by agent
   a. Abrocitinib is FDA-approved for ages 18 years or above. Abrocitinib, however, is approved for ages 12 years or above in Canada.
   b. Baricitinib is not FDA or Health Canada approved for AD. The EMA, however, approved it for AD (https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant).
   c. Upadacitinib is approved for ages 12 years or above.
4. Comorbidities responsive to JAK inhibitors, such as rheumatologic disease or alopecia areata, may lead to patients to favor treating multiple diseases simultaneously with one medication rather than other treatments with efficacy only for AD.
5. Exceptional circumstances that clinicians and patients might consider desirable when not meeting the population criterion of another systemic treatment failing to adequately control severity of AD include the following:
   a. As a brief duration bridge to one of the systemic therapies.
   b. Rare and intermittent use for a severe flare (eg, erythroderma) or for social circumstances (eg, days before a major life event).

Benefits and Harms: The linked systematic review and NMA revealed that the benefits and harms of JAK inhibitors (in alphabetical order), abrocitinib, baricitinib, and upadacitinib, varied by drug and increased with dose of each medication. Figure 5 describes the relative efficacy, presented in greater detail in the linked NMA, across outcomes generally followed, according to daily dose: upadacitinib 30 mg > upadacitinib 15 mg and abrocitinib 200 mg > abrocitinib 100 mg and baricitinib 2 to 4 mg > baricitinib 1 mg.

Although mild and common harms (eg, acne, urinary tract infection, upper respiratory tract infection) increased with the dose of each medication, data addressing less common serious harms were hampered by the short duration of studies (16 weeks typically). For example, although serious infections such as herpetic infections (eg, eczema herpeticum, herpes zoster) were consistently increased in patients with AD using all 3 studied oral JAK inhibitors, there were often no deaths, cancer, or thrombosis detected in the short studies done. The FDA placed a Boxed Warning (a "black box warning") label on almost all JAK inhibitors due to a recent study in rheumatoid arthritis using tofacitinib.

The risk-benefit profile of JAK inhibitors should be considered when selecting JAK inhibitors in clinical practice. Risk considerations should include both observed safety data for the individual drugs from clinical trials of patients with AD, including class-wide theoretical safety concerns and boxed warnings for JAK inhibitors from the US FDA. Published in 2022, the ORAL Surveillance study was a 40-month, randomized, post-authorization noninferiority trial comparing tofacitinib—an oral pan-JAK inhibitor—with tumor necrosis factor (TNF) inhibitor (adalimumab or etanercept) in patients with rheumatoid arthritis enriched for cardiovascular risk (aged 50 years or older with an additional cardiovascular risk factor).[234] Among 4362 participants followed for a median of 4 years, tofacitinib was associated with numerically increased major cardiovascular events (3.4% vs 2.5%), cancer (4.2% vs 2.9% [excludes nonmelanoma skin cancers; lung cancer and breast cancer were the most frequently reported in the trial]), and at higher doses, venous thromboembolism (2.3% vs 0.7%), serious infections (11.6% vs 8.2%), herpes zoster (12.2% vs 4.0%), and death from any cause (2.7% vs 1.2%). Subsequent observational studies in rheumatoid arthritis continue to raise concerns,[235] although the early available nonrandomized data in AD are so far reassuring.[236] Hence, although the increase in herpetic infections—a relatively frequent outcome—is common across both ORAL and the AD population using JAK inhibitors, whether serious harms are shared is uncertain. We found that the included randomized trials seldom encountered serious adverse events, such as deaths, cancer, or thrombosis. Of note, abrocitinib (preferential JAK1 inhibition), baricitinib (preferential JAK1 = JAK2 inhibition), and upadacitinib (preferential JAK1 inhibition) are more selective than tofacitinib (preferential JAK1=JAK2=JAK3 > TYK2 [tyrosine kinase 2] inhibition). In addition, previous epidemiology studies found that patients with rheumatoid arthritis have substantially higher cardiovascular risk compared with those with AD. Finally, the ORAL trial compared tofacitinib with TNF-inhibitors, which were previously found to reduce cardiovascular risk in rheumatologic and gastrointestinal disease. Thus, although the available data produce low-certainty estimates reassuringly near null, they nevertheless contain wide credible intervals that include the potential for harm. There are, as of yet, no robust long-term comparative data in patients with AD using JAK inhibitors, with and without risk factors for these outcomes, to definitively rule out a similar risk applying to them. Although there is high-certainty evidence for benefits to multiple patient-important AD outcomes, this is balanced by low certainty for an increase in patient-important harms.

Values and Preferences: The systematic review of values and preferences[20] and direct patient partner input revealed that patients highly value medications that are both effective and safe, including preferring to avoid adverse effects such as cancer, arterial and venous thrombosis (eg, myocardial infarction, pulmonary embolism, deep vein thrombosis), and serious infections.

The RCT findings addressing benefits and harms (systemic NMA)[19] highlight the values and preferences sensitive decisions that patients with AD and their clinicians will face when key outcome evidence is uncertain. Until randomized trials robustly address such uncertainty, those who place a very high value on reducing symptoms and improving current quality of life and lower value on the uncertain serious harms that some of these agents may cause are likely to choose the most effective interventions (eg, the included oral JAK inhibitors). Those more concerned about avoiding serious harms, and less focused on maximizing symptomatic relief, are likely to choose safer and less-effective interventions (eg, some of the included biologics). The panel therefore inferred that many patients, particularly those where other systemic agents failed to achieve AD control, could put a high value on the high-certainty patient-important benefits that the current systemic JAK inhibitors could provide. Many patients,

Table 6
Some Common Risk Factors for Cancer, VTE, ATE (eg, Myocardial Infarction or Stroke), and Serious Infections

Cancer[177,178]	VTE[179]	ATE[180]	Serious infection
UV light from excessive sun exposure, UV-based treatments, or tanning	Recent major surgery (including hip or knee arthroplasty within 6 wk), injury or trauma	Smoking	Immunocompromised or immunosuppressed
History of chemotherapy or radiation therapy, or large cumulative doses of diagnostic medical radiation	Prior VTE (including travel-associated VTE)	Diabetes mellitus	Unvaccinated status
History of cancer	Active malignancy	Atrial fibrillation	History of serious infections
HIV, EBV, malaria, Hep B, HPV	Pregnancy or postpartum	Peripheral arterial disease	Age
Smoking	Advanced age (eg, >60 y)	Age	
Ethanol use	Estrogen-containing oral contraceptives, hormone replacement, or other estrogen preparations ± NSAID use[181]	Hypertension	
Exposure to less common specific known carcinogens	Obesity	Dyslipidemia	
Cancer-associated inherited syndrome	Thrombophilia (hereditary or acquired [eg, antiphospholipid syndrome])	History of hypertensive disorder of pregnancy (eg, preeclampsia)	
(radon, air pollution, asbestos)	Immobility	Obesity	
Obesity	Female sex	Family history	
	Prolonged travel (air, land) >4 h	Ethnicity	
	Hospital admission	Male gender	
	Central venous catheter	Sedentary	
	Myeloproliferative disorder	Diet	
		Chronic kidney disease	

Abbreviations: ATE, arterial thrombosis; VTE, venous thromboembolism.

however, could place a higher value on avoiding the low certainty for serious harms (death, cancer, venous or arterial thromboembolism, or serious infection). Patients also place a high value on using drugs with a minimal impact on daily activities and the panel inferred that patients may therefore prefer to avoid the screening and monitoring required with JAK inhibitors (described subsequently). Clinicians should therefore engage in shared decision-making to ensure optimal decision making that aligns with values on a case-by-case basis.

Contextual Factors: In general, these drugs are available, albeit even among those with insurance, access can vary due to factors such as high drug cost and variability among individual insurance plans. The Medical Letter on Drugs and Therapeutics summarizes wholesale acquisition costs in 2023.[237] Furthermore, extensive counseling, preinitiation bloodwork, infectious disease treatment and vaccination, and routine blood monitoring while on treatment may lead to prohibitive time required to treat,[186] and limit acceptability, accessibility, feasibility, and equity. Additional patient self-monitoring and the potential for modification of activities or due to comorbidities (eg, that risk thrombosis or infection) may also affect acceptability and feasibility (eg, time, cost).

Summary of Rationale: The panel inferred that most well-informed patients with moderate-severe AD refractory to topical and systemic treatment including either dupilumab or tralokinumab (and possibly in the future, lebrikizumab) would place a greater value on the certain benefits than the burdens and lower certainty for serious harms, but that such values could vary from patient to patient. Such variability and the low certainty for serious harms drove the conditional recommendation.

There may be specific exceptional scenarios where patients will place a high value on very short-term (days) use of oral JAK inhibitors, such as the case of a rare and severe flare or for special social circumstances (eg, days before a major life event such as a wedding) or a brief bridge to safer systemic therapies (eg, dupilumab or tralokinumab).

Implementation Considerations: (Alphabetical) Abrocitinib, baricitinib, and upadacitinib are all immunosuppressants, and therefore, screening for conditions before use (eg, age-appropriate cancer screening, active or latent tuberculosis or viral hepatitis, vaccination including herpes zoster, cytopenias, diverticular disease or bowel perforation, renal and liver function, pregnancy) and subsequent clinician and patient monitoring for adverse effects are required. These can range in severity from acne, abdominal pain, hirsutism, easy bruising, tiredness, and blood abnormalities (lipids and other biochemistries, cell counts) to the serious harms described previously. There are thus multiple implementation considerations, detailed in the eAppendix, including drug-drug interactions, laboratory and clinical monitoring, FDA-approved doses, and practical considerations. Clinicians should consider risk factors for each outcome (Table 6 summarizes some common risk factors).

Recommendation 19: In adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of one of the biologics (dupilumab or tralokinumab) recommended above, the panel recommends against using baricitinib 1 mg daily (strong recommendation, low-quality evidence).

Benefits and Harms: The systematic review and NMA revealed that baricitinib at 1 mg dosing in patients with AD and normal renal function led to the smallest benefits in patient-important AD outcomes across the various doses of baricitinib, abrocitinib, and upadacitinib (and smaller than dupilumab or tralokinumab), and modest compared with placebo (RD for AD severity 7 per 100; quality of life, 7 per 100; itch, 9 per 100; sleep disturbance, 12 per 100; AD flare 3 fewer per 100; Fig 5). Detailed previously in its application to all other oral JAK inhibitors, baricitinib at this dose may cause uncertain but serious harm.

Values and Preferences: As detailed for other JAK inhibitors, the panel inferred from systematic reviews of the evidence and direct patient partner input that patients place a high value on using effective therapies and avoiding serious harms.

Contextual Factors: The potential high incremental burdens and costs did not justify the intervention.

Summary Rationale: The panel inferred that most well-informed patients with AD would place a higher value on avoiding uncertain important harms compared with the moderate-certainty for small, potentially patient-unimportant, benefits of very low dose (1 mg daily) baricitinib.

Implementation Considerations: Baricitinib is renally cleared, and in the presence of chronic kidney disease, the drug monograph suggests to use 1 mg in place of 2 to 4 mg. There are limitations to this approach for AD as there are no direct data to support equivalent clinical effects. Patients and clinicians for which JAK inhibitors

may be the next best treatment option may opt for agents other than baricitinib that rely less on renal clearance (eg, per manufacturer's monograph, upadacitinib levels are not affected by renal impairment).

Azathioprine

Recommendation 20: In patients with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended above, the panel suggests against using azathioprine (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patients who prefer a different adverse effect profile and its required monitoring, and who can wait a longer period of time for symptom relief, may prefer azathioprine over other immunosuppressive agents. For example, although immunosuppressants are generally avoided in pregnancy, methotrexate is absolutely contraindicated and, when required, azathioprine can be used in pregnancy for treatment of systemic lupus erythematosus and inflammatory bowel disease.
2. Patients with risk factors or comorbidities for harms from azathioprine (eg, liver dysfunction) or who place a high value on avoiding other harms (eg, gastrointestinal adverse effects) may place a greater value on avoiding these potential harms compared with azathioprine's possible benefits.
3. The availability and value placed by patients and caregivers on other systemic treatment alternatives may influence decision making.
4. Patients with comorbidities, such as rheumatologic and autoimmune diseases, may prefer to use azathioprine to address more than one condition, compared with other treatments that do not address such comorbidities.

Benefits and Harms: The linked systematic review and meta-analysis revealed modest benefits across patient-important AD outcomes (Fig 5, RD for improvement in AD severity of 4 per 100; of quality of life 8 more per 100). Most outcomes, however, were low-certainty. Harms recognized with azathioprine include leukopenia, pancreatitis, and a possible increased risk of cancer.

Values and Preferences: The linked systematic review[20] revealed that patients highly value safe and effective medications that have a low impact on daily activities. The panel inferred that most well-informed patients would place a high value on avoiding harms and burdens associated with azathioprine.

Contextual Factors: Pretreatment blood screening (eg, thiopurine methyltransferase [TPMT] testing) to minimize the risk of azathioprine harms (eg, neutropenia) and subsequent routine laboratory monitoring are likely to place increased burdens on patients and consume more resources.

Summary Rationale: The panel inferred that most well-informed patients would place a high value on avoiding the uncertain harms and added burdens with azathioprine compared with the modest benefits in 2 of 5 patient-important AD severity outcomes (clinician-reported severity [moderate certainty] and patient-reported itch [low certainty]). The absent or low certainty of evidence addressing outcomes critical to decision-making and close balance of benefits and harms drove the conditional recommendation.

Implementation Considerations: The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Cyclosporine (Cyclosporin, Ciclosporin)

Recommendation 21: In patients with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously, the JTF panel suggests replacing cyclosporine as the systemic treatment over continued topical and systemic standard care (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Cyclosporine has conventionally been administered at either low (2-3 mg/kg) or high doses (4-5 mg/kg). Whether to start at a low dose and titrate up to effect, or to start at a high dose and titrate down, depends on multiple factors, including the patient's disease severity at the time and the patient's desired rapidity of effect balanced by the increased risk of harm with higher doses. Patients should be on the lowest dose possible that achieves patient-important benefit and minimizes harms.
2. The availability and/or value placed by patients/caregivers on other safer systemic treatment alternatives may influence decision-making.
3. Patients with risk factors or comorbidities for harms from cyclosporine (eg, cardiovascular risk factors, difficult to control hypertension, renal dysfunction), or who place a high value on avoiding possible hypertrichosis or gum hypertrophy may place a greater value on avoiding these potential harms compared with cyclosporine's probable benefits.
4. Patients should not be required to develop adverse events from cyclosporine or to first undergo a trial of it before using safer and more effective alternatives (eg, dupilumab or tralokinumab).
5. Exceptional circumstances that clinicians and patients might consider desirable when not meeting the population criterion of another systemic treatment failing to adequately control severity of AD include the following:
   a. As a brief duration bridge to one of the systemic therapies
   b. Rare and intermittent use for a severe flare (eg, erythroderma) or for social circumstances (eg, days before a major life event).

Benefits and Harms: The linked systematic review and NMA revealed that cyclosporine may improve patient-important AD outcomes in a dose-dependent fashion (Fig 5, eg: low-dose cyclosporine for improvement in AD severity, RD 6 per 100; quality of life RD 16 per 100; itch RD 12 per 100).

Direct evidence for harms in AD is uncertain, although indirect evidence from a NMA of RCTs in patients with psoriasis revealed an increase in adverse events.[238] The most common recognized with cyclosporine are nephrotoxicity, both reversible and irreversible, and hypertension. More serious adverse effects—death, cancer, and cardiovascular events—were sparsely reported and not adequately addressed by the AD data. In adult patients receiving a renal transplant, a 230 patient RCT revealed dose-dependent increase in cancer risk, starting at 2 years, and increasing in 7 years.[239] The most common cause of death in that RCT was cancer. The evidence for benefits with cyclosporine was low for most outcomes due to serious imprecision and risk of bias. The evidence for harm was low or very low due to serious indirectness and serious imprecision.

Values and Preferences: The linked systematic review of patient values and preferences[20] and direct patient input revealed that patients value therapies that are both effective and safe, that have a minimal impact on daily activities, and to step up therapy according to disease severity. The panel inferred that most well-informed patients would place a higher value on the uncertain patient-important benefits over the uncertain common harms and burdens and uncertain rare long-term serious harms.

Contextual Considerations: Cyclosporine requires blood pressure and blood test (kidney function) monitoring which may limit acceptability, accessibility, feasibility, and equity.

Summary Rationale: The panel inferred that most well-informed patients would place a higher value on the uncertain patient-important benefits compared with the more certain modest common

harms and the very low certainty for serious long-term harms. The anticipated variability in patient values and preferences, low-certainty evidence, and resource implications drove the conditional recommendation.

Implementation Considerations: The longest duration to use cyclosporine that is safe is not clear, although patients are often transitioned to other maintenance therapies within 1 to 2 years. The efficacy and safety of cyclosporine combined with other systemic treatments is uncertain.

Multiple ideal body weight calculators are available for dosing. The eAppendix provides additional practical information and implementation considerations, including examples of blood pressure, renal function, and other monitoring, in 1-2 page handouts. Although there may be differences between modified (microemulsion generic drug, eg, Neoral or Gengraf brand names) and unmodified (generic or Sandimmune brand name) formulations of cyclosporine, a small randomized trial in patients with AD provides low certainty evidence for little to no difference between Neoral and Sandimmune cyclosporine formulations.[240] The 2 formulations are converted between each other at 1:1 dosing. Similar data are found in comparison of formulations in treating patients with psoriasis[241] and rheumatoid arthritis.[242,243] Indirect evidence from randomized trials in organ transplant,[244-248] nonrandomized studies addressing AD and rheumatologic conditions, and pharmacokinetics studies suggest that modified (microemulsion) formulations of cyclosporine, designed to produce higher and more consistent drug levels (bioavailability), may lead to more rapid time to effect, potentially larger treatment effects, albeit often in ranges of magnitude of uncertain patient importance, and lower risk of harm.[249-254]

Methotrexate

Recommendation 22: In patients with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously, the panel suggests against using methotrexate (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patients who prefer a different adverse effect profile and its required monitoring, and who can wait a longer period of time for symptom relief, may prefer methotrexate over other immunosuppressive agents.
2. Methotrexate is contraindicated in pregnancy and should not be used for patients, both male and female, intending to conceive.
3. Patients with risk factors or comorbidities for harms from methotrexate (eg, liver dysfunction) or who place a high value on avoiding adverse effects (eg, stomatitis, abdominal pain) may place a greater value on avoiding these potential harms compared with methotrexate's possible benefits.
4. The availability and value placed by patients and caregivers on other safer systemic treatment alternatives may influence decision making.
5. Patients with comorbidities, such as rheumatologic and autoimmune diseases, may prefer to use methotrexate to address more than one condition, compared with other treatments that do not address such comorbidities.

Benefits and Harms: The systematic review and NMA revealed that modest benefits with add-on methotrexate compared with continued standard care in 2 patient-important AD outcomes (Fig 5; AD severity RD 6 per 100; quality of life 10 per 100) and other outcomes were very uncertain due to extremely serious imprecision.

Although serious adverse events were uncommon, existing RCTs in cardiovascular disease, psoriasis, psoriatic arthritis, and inflammatory bowel disease reveal probably no important increase in mortality in 1 to 2 years. The Cardiovascular Inflammation Reduction Trial was a 5-year RCT with 4786 patients with known cardiovascular disease and diabetes or metabolic syndrome, which found that 87% of patients taking methotrexate experienced an adverse event, compared with 82% of patients taking placebo (HR 1.17 [95% CI, 1.10-1.25]). Methotrexate increased risks for skin cancer (2%), gastrointestinal (RD 3%), infection (RD 4%), pulmonary (RD 3%), and hematologic adverse events (RD 18%).[255] In a meta-analysis of 68 trials (6938 patients), methotrexate, compared with placebo or standard care, increased the risk of one or more adverse events (RR 1.13 [95% CI, 1.04-1.22]).[256] The certainty of the evidence was low for the AD severity and quality of life due to serious risk of bias and imprecision. Other AD outcomes were very low due to extremely serious imprecision. Harms were rated moderate certainty due to serious indirectness.

Values and Preferences: On the basis of the linked systematic review of patient values and preferences[20] and direct patient partner input, the panel inferred that most well-informed patients would value avoiding the uncertain modest benefits and more certain harms.

Contextual Factors: Methotrexate, similar to most other immunosuppressants, requires screening at baseline and routine blood monitoring. On average, methotrexate may cost less compared with other immunosuppressants and, particularly when costs are borne directly by the patient, could then play a more important role in decision-making.

Summary Rationale: The panel inferred that most well-informed patients would prefer to avoid the modest benefits (with slow onset) and more certain harms and burdens associated with methotrexate use compared with continued standard care, or alternative, more effective options. The low-certainty evidence, close balance of benefits and harms, and anticipated variability in patient values and preferences drove the conditional recommendation.

Implementation Considerations: The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Mycophenolate Mofetil (Mycophenolic Acid)

Recommendation 23: In patients with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously, the panel suggests against using mycophenolate (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patients who prefer a different adverse effect profile and its required monitoring, and who can wait a longer period of time for symptom relief, may prefer mycophenolate over other immunosuppressive agents.
2. Mycophenolate is contraindicated in pregnancy and should not be used for patients intending to conceive.
3. Patients with risk factors or comorbidities for harms from mycophenolate (eg, renal or liver dysfunction) or who place a high value on avoiding possible other harms (eg, gastrointestinal adverse effects) may place a greater value on avoiding these potential harms compared with mycophenolate's uncertain benefits.
4. The availability and value placed by patients and caregivers on other safer systemic treatment alternatives may influence decision making.
5. Patients with comorbidities, such as rheumatologic and autoimmune diseases, may prefer to use mycophenolate to address

more than one condition, compared with other treatments that do not address such comorbidities.

Benefits and Harms: The systematic review and NMA revealed that the evidence for mycophenolate being beneficial in AD was sparse and only for modest improvement in one patient-important outcome, AD severity (RD 8 per 100) and was low in certainty (Fig 5).

There were no cancers or serious infections reported in the included studies. Mycophenolate, for any indication, is associated with increased cancer and serious infection risk. Robust data from different populations (autoimmune disease, transplant, skin diseases) are, however, sparse and therefore of also low certainty when applied to AD.

Values and Preferences: On the basis of the linked systematic review of patient values and preferences[20] and direct patient partner input, the panel inferred that most well-informed patients would value avoiding the uncertain modest benefits and more certain harms.

Contextual Factors: Mycophenolate, similar to most other immunosuppressants, requires screening at baseline and routine blood monitoring.

Summary Rationale: The panel inferred that most well-informed patients would place a higher value on avoiding the uncertain important harms compared with the uncertain modest benefits, especially when considering safer or more certain alternatives. The low-certainty evidence drove the conditional recommendation.

Implementation Considerations: The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Narrow-Band UV-B Light

Recommendation 24: In patients with moderate-severe AD refractory, intolerant, or unable to use mid- to high-potency topical treatment and systemic treatment inclusive of a biologic recommended previously, the JTFPP panel suggests adding clinic-based narrow-band UV-B treatment (conditional recommendation, low-certainty evidence).

Conditions to consider:

1. Patients who prefer a different adverse effect profile, or to avoid immunosuppressant medications and their required monitoring (no blood monitoring in this instance), and who desire more rapid symptom relief may prefer NB-UVB over other treatments. For example, patients who are pregnant or planning to become pregnant may prefer NB-UVB.
2. NB-UVB can be difficult to access, and hence, patients who must travel large distances, incur costs (eg, parking, gas, time), or face long wait times may prefer other treatments over NB-UVB.
3. Patients with photoresponsive comorbidities, such as psoriasis or vitiligo, may prefer to use NB-UV-B to address more than one condition, compared with other treatments with efficacy only in AD.
4. Conversely, patients who also have photosensitive conditions, photodermatoses, or risk factors or a history of skin cancer may prefer to not use phototherapy.
5. Exceptional circumstances that clinicians and patients might consider desirable when not meeting the population criterion of topical treatments and a systemic treatment failing to adequately control AD include accessing NB-UVB for the patient is highly convenient and cost-effective.

Remark: The panel did not formally develop recommendations for other forms of phototherapy (also known as light therapy), such as UV light A band (UV-A) alone or with psoralen (PUVA), as UV-A –based therapies are associated with more harms and have even lower certainty for benefits in AD (systemic treatment NMA[19] and Cochrane review[257]).

Although the panel suggested oral JAK inhibitors, cyclosporine or NB-UV-B in this population, they did not yet issue a formal recommendation addressing one over the other. Patients, however, will likely pursue only 1 of these 3 therapies. There are, as of yet, no robust studies addressing combination therapy, and hence, shared-decision making should address scenarios where combination therapy might be considered (eg, patients refractory to any 1 of the 3 interventions).

Benefits and Harms: The linked systematic review and NMA revealed that clinic-based NB-UV-B improved AD severity (RD 5 per 100), itch (12 more per 100), and sleep disturbance (27 more per 100), but that the available evidence did not address quality of life, flares, or serious adverse events (Fig 5).

Harms were not captured by most studies. There were no cancer events reported in studies. A 10-year cohort study in Korea including 60,321 patients with vitiligo found no increased risk of nonmelanoma or melanoma skin cancer, stratified by number of sessions (from <50 to >500). An analysis of a Scottish cancer registry of 3867 patients made the same conclusion. The cohort study from Korea addressing vitiligo, however, found an increased risk of actinic keratosis for patients who had undergone more than 200 sessions (HR, 2.27 [95% CI, 1.53-3.37]). A common adverse event is erythema. Clinical experts remarked that long-term UV-B exposure might induce darkening of the skin and that this may, or may not, be desirable for patients.

Certainty of evidence for AD severity and sleep disturbance were low due to very serious imprecision (small sample sizes and wide CIs), and itch, moderate due to serious imprecision. The evidence for harms was low due to being observational in nature.

Values and Preferences: The linked systematic review of patient values and preferences[20] and direct patient input revealed that patients place a high value on interventions that are minimally disruptive to their daily activities. They also value interventions that are both safe and effective. NB-UV-B, requiring going to a clinic 3 times a week, may not align with these values for many patients.

Contextual Factors: Attending a clinic 3 times per week for prolonged periods may be challenging for many patients with AD and their caregivers and can incur significant direct and indirect costs. In a Boston, USA, study, travel distance greater than 5 miles was associated with nonadherence (adjusted OR, 2.06 [95% CI, 1.30-3.26]).[258] Centers with NB-UV-B devices may not be equally accessible by most patients with AD.

Summary Rationale: The panel inferred that most well-informed patients with moderate-severe AD refractory to other systemic treatments would place a higher value on the uncertain important improvements in AD severity, itch, and sleep disturbance over the uncertain modest harms and important practical issues.

Implementation Considerations: The eAppendix provides expanded discussion about practical considerations. The National Eczema Association provides a patient handout addressing phototherapy: https://nationaleczema.org/eczema/treatment/phototherapy/. Although NB-UV-B is also available using home devices, they lack robust evidence addressing their efficacy and safety, and comparability with clinic-based NB-UV-B, for treating AD. Clinical experts, however, noted that some insurance plans will cover this for patients and that patients find home-based therapy convenient.

Systemic Corticosteroids

Recommendation 25: In patients with atopic dermatitis, the JTF panel suggests against using systemic corticosteroids (conditional recommendation, low-certainty evidence).

Benefits and Harms: The linked systematic review and NMA revealed that systemic corticosteroids improved AD severity but had

little to no improvement in quality of life, itch, or sleep disturbance[14] (Fig 5). Hence, the benefits were low certainty due to very serious imprecision. The trials often reported that benefits were transient and disease activity rebounded on systemic corticosteroid discontinuation.

The included studies did not report many adverse events. Common adverse events in patients with AD using systemic corticosteroids include rebound flares shortly after drug discontinuation, weight gain, insomnia, adrenal insufficiency, and growth impairment.[259,260] Less than 30 days of oral corticosteroids, for any indication, is associated with sepsis (IRR, 5.3 [95% CI, 3.80-7.41]; 5 vs 1 per 1000), venous thromboembolism (IRR, 3.33 [2.78-3.99]; 8 vs 2 per 1000), and fracture (1.87 [1.69-2.07]; 27 vs 14 per 1000).[259] Clinical experts reported that they often see patients undergoing repeated cycles of systemic corticosteroids rather than accessing safer and more effective long-term AD control strategies. For multiple indications, repeated cycles of short-term (<7 days) systemic corticosteroids and long-term systemic corticosteroid use cause a range of common and serious harms.[259-263] Adverse effects of repeated use include fragility fractures secondary to osteoporosis, heart attack/stroke, diabetes, and obesity.

Values and Preferences: The linked systematic review[20] and direct patient input revealed that patients value rapid-acting interventions that are both safe and effective. Although systemic corticosteroids may be both rapid acting and effective, the panel inferred that their transient benefit and risk for adverse events (including repeated or prolonged cycles of systemic corticosteroids) did not align with most patients' values and preferences.

Contextual Factors: The harms associated with repeated systemic corticosteroid use, including their association with obtaining them through the emergency department, urgent care centers, or urgent clinician visits, consume more resources.

Summary Rationale: The panel inferred that most well-informed patients would place a higher value on avoiding harms and poor long-term AD control with systemic corticosteroids vs their uncertain important benefits. The significant harms and burdens in relation to their often transient benefit and low certainty evidence drove the conditional recommendation. Their existing overuse[264] supported against their routine use for flare management or bridge therapy. The eAppendix provides additional practical information and implementation considerations in 1-2 page handouts.

Mechanisms of Action of Systemic Treatments

Moderate-severe AD can be refractory to topical treatments, so systemic agents may be needed to achieve disease control.

Dupilumab is a humanized monoclonal antibody (mAb) that binds the IL-4 receptor alpha subunit. By specifically targeting IL4Rα, it inhibits IL-4 and IL-13 signaling to reduce cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE. IL-4 and IL-13 drive the type 2 inflammation in AD.[265-267]

Tralokinumab is a humanized IgG4 monoclonal antibody that specifically binds to IL-13 inhibiting its ability to bind receptors.[268] IL-13 is a pleiotropic T_H2 cytokine that contributes to skin barrier disruption, inflammation, increased risk of skin infections, itch signaling, and epidermal hyperplasia.

JAKs are key components of the JAK/STAT pathway for cytokine receptor signaling which is an integral part of the inflammatory pathophysiology of AD.[269] JAK1 has an important role in signaling through IL-4, -5, -13 and -31, cytokines associated with AD inflammation. In addition, JAK1 is important in signaling of other cytokines including IL-2, IL-6, IL-7, IL-9, and IL-15 which are critical for a variety of immune functions.[270] Baricitinib is a selective inhibitor of JAK1 and JAK2. Second-generation JAK inhibitors have increased selectivity; abrocitinib and upadacitinib selectively inhibit JAK1. These are small molecule agents, so systemic adverse effects are of concern. Increased selectivity of the second-generation agents may reduce associated adverse events.[271]

Azathioprine is a purine synthesis inhibitor that reduces leukocyte proliferation. Azathioprine interferes with T-cell, B-cell, and antigen-presenting cell functions.[272]

Cyclosporine is an immunomodulatory medication that inhibits IL-2 signaling and the function of T lymphocytes through a complex formed between cyclosporine and cyclophilin.[273] Suppression of IL-2 inhibits calcineurin and signal transduction mediated by T-cell receptor activation and in AD, down-regulation of levels of T_H2-, T_H22-, and some T_H17-related molecules (ie, IL-13, IL-22, CCL17, S100As, and elafin/peptidase inhibitor 3), and modulation of epidermal hyperplasia and differentiation measures.[274]

Methotrexate is an antimetabolite that interferes with folic acid metabolism, leading to repression of immune cell activation by multiple mechanisms.[275]

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine-5′-monophosphate dehydrogenase. MPA depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation. MPA also inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation. MPA depletes tetrahydrobiopterin and decreases the production of nitric oxide by inducible nitric oxide synthase, and subsequent oxidative radicals, by activated macrophages.[276-278]

NB-UV-B reverses epidermal defects and alters the cutaneous inflammatory milieu.[279,280]

Limitations of These Guidelines

Limitations of these guidelines include focusing on the most common aspects of AD care. In particular, we did not address Traditional, Complementary, or Integrative medicines[281] or Indigenous Ways of Knowing.[116] If these interventions or others become more frequently used, we aim to address them in subsequent living guidelines in which individual recommendations are updated or added as new evidence arises. Future research may provide robust evidence regarding these interventions.

AD, similar to many other medical fields, lacks robust evidence for safety of medications during pregnancy and breastfeeding. Well-conducted studies to address this population are critically required. Another issue is that many trials in AD are placebo controlled, which may be most appropriate during early drug development, but specific funding and investigations must be promoted—through professional organizations, government organizations (eg, National Institutes of Health/National Institute of Allergy and Infectious Diseases), and private organizations—to promote comparative effectiveness and safety of approved medications and their optimal use in treatment pathways. Robust data addressing patients who are pregnant, and that, in general, address comparative effectiveness may inform future guideline recommendations.

Recommendations for Future Research

By reviewing the cumulative data addressing AD to date, the panel made 22 key research recommendations. The Guideline main text and eAppendix address research needs for specific interventions.

Optimize Study Designs

1. Stop split-body studies (where different parts of an individual patient's body are randomized to different treatments and disease activity at each site is compared against each other). These have significant limitations including being unable to adequately assess adverse events, equally important to efficacy assessments,

and ignore the systemic inflammation[282,283] and impact of AD for patients.

2. Limit, if not stop, crossover studies. These designs are suboptimal as there are almost always challenges in interpreting whether carryover or period effects occur. Harms should be equally evaluated to benefits. Any such studies should report effects by period and have long washout periods that account not only for washout for efficacy but also washout for potential harms. Such longer trial periods may negate the often overemphasized efficiency gains from recruiting fewer participants in crossover studies.
3. Studies addressing induction of remission should be at least 4 weeks in length. Those that incorporate continued use of an intervention with the objective to sustain/maintain disease control, or that represent pragmatic disease management strategies, should be at least 1 year in duration. Limiting the burden of interventions and trial participation will be essential to study retention.
4. The comparator in RCTs must be standard of care with or without an added active comparator. Prohibiting treatments that would otherwise be used during routine clinical care, for example, TCSs, TCIs, and emollients, deprives patients of standard care, exaggerates treatment responses, and does not reflect what patients will experience in routine clinical practice. Active comparators are preferable (eg, biologic vs biologic; or biologic vs small molecule inhibitor or other whole-body therapy including phototherapy).

Improve Data Collection, Analysis, and Reporting

5. Investigators must report all studies, including multiple-ascending dose and safety studies, in full and on a trial-by-trial basis. If a report presents pooled analyses of multiple RCTs, the individual trial results before pooling should be reported completely as part of the full publication, regardless of whether or not the pooling was prespecified.
6. All conference abstracts or publications that are subanalyses must clearly report the parent main trial registration number (eg, NCT) and main publication citation, specifying which data, if any, are unique to the subanalyses in comparison to what was already reported in the main publication.
7. Participants randomized more than once should have their data reported per randomization. For example, if patients were randomized and assigned to group A until week 16, then rerandomized to group B from week 16 to 52, investigators should separately report baseline and outcome data for participants from weeks 0 to 16 assigned to group A, then separately for the same participants assigned to group B from weeks 16 to 52 and should clearly report characteristics of participants in both periods. Should there be participants who receive the same intervention in both periods (eg, from the example previously, the same intervention from weeks 0 to 52), investigators should clearly report the outcome data for this subgroup of participants. Rerandomized participants' outcome data should be reported in isolation, before separate analyses that pool them with those participants who did not undergo rerandomization.
8. Studies should report, in tabular format, the mean values, SD, and number of participants analyzed, the number missing (including if they were imputed for the analysis), for baseline, each analyzed time point, and absolute change from baseline values of all continuous outcomes. The change from baseline value should clearly report how it was calculated and whether all corresponding statistical assumptions are met (eg, no baseline by treatment interaction in ANCOVA [linear mixed] models). ANCOVA, or similar regression-based models, with change from baseline as the outcome variable and covariates at minimum being baseline value and treatment group assignment should be considered for statistical analyses of continuous outcomes. Additional analyses such as responder analyses (eg, EASI75, SCORAD50) should be part of the main trial report, but should be reported in addition to, not as a replacement for, the continuous outcome data. Other analyses such as percentage change from baseline can be reported as supplementary data.
9. All studies should report patient baseline characteristics and the baseline values for any outcome data (eg, baseline EASI, SCORAD, POEM, itch, sleep disturbance, and quality of life).
10. All publishers should mandate submission of the formal clinical trial protocol and statistical analysis plan with any manuscript submission reporting a clinical trial. Trial reports should fully adhere to CONSORT reporting guidelines.
11. All studies completed or terminated early by investigators (pharmaceutical companies or investigator initiated) should publish their findings and upload outcome data to public clinical trial registers (eg, clinicaltrials.gov). Enforcement must be at multiple levels. For example, in March 2023, the United Kingdom legislated a requirement for the public disclosure of clinical trial data within 12 months of trial completion; otherwise, the sponsor cannot continue to conduct any more registered trials (https://www.gov.uk/government/consultations/consultation-on-proposals-for-legislative-changes-for-clinical-trials).
12. All studies should be analyzed for efficacy by analyzing all patients by the treatment group they were originally assigned to, regardless of their adherence or crossover (what is frequently referred to, but often ambiguously or erroneously described, as intention-to-treat). It should be made explicit how many are analyzed at each time point, and in the presence of missing data, how many were imputed.
13. Any report of an interim analysis must report the initial planned full trial size, and what proportion (%) is being represented in the current report, and whether the interim analysis was done with or without first analyzing any outcome data.
14. Mechanistic outcomes should be reported separately from studies of clinical outcomes because mechanistic outcomes and clinical outcomes often have different measurement methods, requirements (and scientific cultures) in reporting and data presentation, and it can be challenging to satisfy requirements of both fields of study. These separate reports of mechanistic outcomes should nevertheless be explicitly linked to the parent study by referencing the trial registration number and highlighting this link in the abstract and methods.
15. Formal time-to-event methods should be used for time-to-response to therapy at minimally important differences (eg, NRS4, EASI50, or obtaining and maintaining a specific severity strata) rather than multiple checks of dichotomous outcomes if claims of time-to-event are going to be made. Such methods must account for intrapatient variability, including both losing and regaining, the response threshold.

Focus on Patient-Important Benefit and Harm Outcomes

16. In some cases of outcome assessment, there are multiple minimally important differences reported but it is not clear which is the most credible. For other outcome measures, such as sleep disturbance scales captured as part of SCORAD or long-term control with RECAP, minimally important differences require quantification.
17. Reprioritization of outcomes is needed. Less outcomes per study should be collected and more focus should be placed on assessing patient-important ones, for example, patient-reported severity (such as by POEM), AD-related quality of life, flares (such as

captured by RECAP), itch, sleep disturbance, and harms, and less so IGA.

18. Where there are treatment safety concerns, studies should be of sufficient length to, at least, address cancers and thrombosis, that is, robust multiyear comparative studies. The framework addressing the safety of TCIs presented in the Guideline main text, along with the eAppendix, provides additional study design considerations.
19. Adverse events (AEs) such as worsening of AD, and in particular, discontinuations or moderate and severe AEs due to treatment-induced harms, must be differentiated from all other AEs. Owing to the relapsing nature of AD, studies should separate adverse reactions from worsening of preexisting AD (or its known complications such as localized infections) as this obfuscates assessment of treatment-specific harms (eg, placebo experiences more AEs due to worsening AD, whereas the intervention may improve in AD and therefore the study end up reporting that the treatment group, compared with the placebo group, had less overall AEs). This further reinforces the need for active comparator trials.

Actively Promote Equity, Diversity, and Inclusiveness in Clinical Trials and Research Addressing Atopic Dermatitis

20. All patients with AD deserve to access novel medicines and randomized trials, yet racial and ethnic underrepresentation is common in current AD trials[284,285] and historically racialized groups are often suboptimally reported.[286] Active engagement and outreach to equitably include diverse populations are needed in future AD RCTs and research. Reporting of race and ethnicity should follow updated standards.[88,287]
21. The word "subjects" should be abandoned in all future clinical research reports. The word subject, particularly in a modern context, has negative implications for equity, diversity, and inclusiveness, and historical adverse connotations regarding unethical experimentation in marginalized populations such as African American and Indigenous Peoples. Patients contribute a lot in partaking in research and their engagement is crucial to understand how to achieve optimal health outcomes. Hence, they should appropriately be referred to as "patients," "participants," or "individuals."

Reconsider the Definition of Disease Severity and Control in Atopic Dermatitis

22. In its current use, most AD severity (eg, IGA, EASI) addresses a single assessment in time of a patient's experience, and that experience is often inferred based on a clinician's determination of patient signs. However, severity in other allergic diseases, such as asthma, typically refers to the intensity of therapy required to achieve and maintain disease control, along with classifications regarding risk for future exacerbation and risk for future AEs.[288] The conceptualization of AD management could be reframed. The JTF AD Guideline group may expand upon this concept in future publications.

What Is New in These American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters Atopic Dermatitis Guidelines and What Are Others Saying?

This JTFPP AD guidelines represent an evolution[231,289-293] in trustworthy allergy guidelines[1] and are distinguished from other guidelines[2,3] through systematic reviews of the evidence with multidisciplinary panelist engagement, adherence to a rigorous guideline development process, the involvement of the patient and caregiver voice from start to finish, clear translation of evidence to clinically actionable and contextual recommendations, and novel approaches to facilitate knowledge translation. The guidelines emphasize, in addition to standards of trustworthiness, the third principle of evidence-based medicine: that evidence alone is never enough; that patient values and preferences are crucial to arriving at optimal recommendations.[7,8]

The current guidelines also differ from our previous guidelines in other ways. The 2012 Atopic Dermatitis Practice Parameter[9-11] covered a wide range of topics including immunopathology, diagnosis, and trigger factors and was a revision of the 2004[12] and 1997 guidelines[13]; the 2023 guidelines focus on 5 main questions addressing therapy. The 2012 guidelines used a now-outdated rating of the medical evidence using categories of evidence to determine the strength of recommendation (A, B, C, D)[7,122]; 2023 used GRADE (recommend for, suggest for, suggest against, recommend against), fulfilled explicit requirements for claiming proper use of GRADE,[4] and followed trustworthy guideline principles, including explicit management of potential conflicts of interest, consideration of equity, diversity, and inclusiveness, multistakeholder involvement, and emphasis on including the patient voice in shaping recommendations. Since the publication of the 2012 guidelines, multiple new therapies have emerged including multiple biologics, small molecules, and a topical PDE4 inhibitor. These are well covered in the 2023 guidelines. The 2023 update provides more guidance on shared decision-making and practical issues to consider as well. The JTF guidelines incorporate the expert opinion provided in the atopic dermatitis yardsticks.[294,295]

The European Dermatology Foundation recently published a guideline on systemic therapy in AD on a website its Living EuroGuiDerm guideline for the systemic treatment of atopic eczema.[296] This guideline was developed at 4 consensus conferences from December 2020 to July 2021. The website lists multiple topics and recommendations on AD. In comparing the recommendations, both the JTFPP and EuroGuiDerm guidelines give strong recommendations for dupilumab and tralokinumab. The EuroGuiDerm guideline also strongly recommends cyclosporine and the 2 JAK inhibitors approved in Europe, baricitinib and upadacitinib, whereas the JTF guideline gives, due to the balance of benefits and harms, low certainty for serious harms, and considering patient values and preferences and contextual factors, conditional recommendations to these interventions, thereby encouraging shared decision-making. Similarly, the EuroGuiDerm guideline provides weak (conditional) recommendations in favor for azathioprine, methotrexate, and systemic glucocorticosteroids, whereas the JTF guidelines, due to the balance of benefits and harms, low-certainty evidence, and considering patient values and preferences and contextual factors, conditionally recommend against these interventions.

Revision or Adaptation of the Guidelines

After publication of these guidelines, the JTF will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions as living guidelines.[297] This may include, for example, formal assessment of lebrikizumab (anti–IL-13), nemolizumab (anti–IL-31), tapinarof (aryl hydrocarbon receptor agonist), asivatrep (transient receptor potential vanilloid subfamily member 1 [TRPV1] antagonist), roflumilast (PDE-4 inhibitor) or other treatments, and consideration of robust comparative long-term safety data of topical and systemic JAK inhibitors.

Updating or adapting recommendations locally: Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated evidence-to-decision frameworks detailed throughout the Guideline main text. The eAppendix may be adpated as necessary.

The epidemiology, pathophysiology, clinical evidence, and patient testimonials[298] reveal that AD is a systemic disease affecting patients and caregivers. The AAAAI/ACAAI JTF guidelines support achieving optimal outcomes in AD.

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Supplementary materials

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