Title

Atopic Dermatitis (Eczema) Guidelines: 2023 AAAAI/ACAAI Joint Task Force (JTF) on Practice Parameters GRADE- and Institute of Medicine-based recommendations

Authors

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Disclosures

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Abstract

Background: Atopic dermatitis (AD) is among the most common skin disorders worldwide, often starts early in life, and is associated with significant impairments in quality of life and economic burden. Guidance addressing disease management, was last issued in 2012 by the American Academy of Allergy, Asthma, and Immunology (AAAAI) and American College of Allergy, Asthma and Immunology (ACAAI) Joint Task Force (JTF) and requires updating in terms of both evidence and 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 convened, comprised of patients and caregiver partners, experts in AD (dermatology and allergy/immunology), primary care clinicians (family medicine, pediatrics, internal medicine), and allied health professionals (psychology, pharmacy, nursing) prioritizing equity, diversity, and inclusiveness and implementing management strategies to minimize influence of conflicts of interest. The McMaster Evidence in Allergy Group supported the guideline-development process, including performing systematic evidence reviews and holding focus groups with patient and family partners. The panel prioritized clinical questions and outcomes according to their importance for patient and family care. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach informed rating the certainty of the evidence, and Evidence-to-Decision frameworks, which were subject to public comment, translated evidence to recommendations using trustworthy guideline development principles.

Results: The panel agreed on 25 treatment recommendations to gain and maintain control of AD for patients with mild, moderate, and severe AD. Strong recommendations included adding topical corticosteroids and/or topical calcineurin inhibitors for patients refractory to moisturization alone, and, after initial control of AD is achieved, address relapsing disease with continued intermittent therapy (proactive therapy), and in patients with moderate-to-severe disease refractory to this, adding dupilumab or tralokinumab biologics. Conditional recommendations included applying mid-potency topical agents once rather than twice daily, wet wrap therapy or crisaborole if aligned with patient values and preferences, not starting with topical JAK inhibitors as first-line therapy, and, depending on disease severity, adding bleach baths and allergen immunotherapy but not dietary avoidance (elimination diets with or without allergy skin testing) nor systemic corticosteroids. Among patients refractory to topicals and biologics, the panel provided multiple conditions to consider for optimal treatment selection, including oral JAK inhibitors, cyclosporine, or light therapy, to align with patient values, preferences and individual circumstances. A good clinical practice statement overarches these recommendations to ensure optimal diagnosis, patient engagement, and foundational therapy. The Appendix provides additional details, practical information and implementation considerations in 1-2 page patient-friendly handouts.

Conclusions: These evidence-based recommendations comprehensively address optimal use of (1) topical treatments (barrier moisturization devices, corticosteroids, calcineurin inhibitors, PDE4 inhibitors [crisaborole], occlusive [wet wrap] therapy, adjunctive antibiotics, frequency of application, maintenance therapy), (2) dilute bleach bathing, (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 ultraviolet phototherapy (light therapy). The panel also identified key future research needs. This guidance document will be updated periodically.

KEYWORDS

Atopic dermatitis (eczema) guidelines; AAAAI/ACAAI Joint Task Force on Practice Parameters (clinical practice guideline); evidence-based medicine; GRADE strong and conditional recommendations; shared-decision making; patient values and preferences; multidisciplinary; topical corticosteroids; topical calcineurin inhibitors; topical Janus kinase (JAK) inhibitors; topical PDE4 inhibitors (e.g. crisaborole); wet wrap therapy; frequency of application; proactive and reactive topical therapy; barrier moisturizer devices; topical antibiotics/antiseptics; biologics and monoclonal antibodies; small molecule immunomodulators; phototherapy (light therapy); systemic corticosteroids; induction and maintenance of eczema remission; research needs and knowledge gaps; severity strata (bands); potency; network meta-analysis

ABBREVIATIONS

AAAAI, American Academy of Allergy, Asthma and Immunology
ACAAI, American College of Allergy, Asthma and Immunology
JTFPP, Joint Task Force on Practice Parameters
AD, atopic dermatitis
RCT, randomized clinical trial
TCS, topical corticosteroid
TCI, topical calcineurin inhibitor
PDE4i, phosphodiesterase 4 inhibitor
JAKi, Janus Kinase inhibitor
AIT, allergen immunotherapy
SCIT, subcutaneous immunotherapy
SLIT, sublingual immunotherapy
HDM, house dust mite
NB-UVB, narrow-band ultraviolet B light
MD, mean difference
OR, odds ratio
RR, risk ratio
RD, absolute risk difference
CI, confidence interval
CrI, credible interval
GRADE, Grading of Recommendations Assessment, Development and Evaluation
EASI, Eczema Area and Severity Index
SCORAD, SCORing Atopic Dermatitis
POEM, Patient-Oriented Eczema Measure
VAS, visual analogue scale
NRS, numeric rating scale;
DLQI, Dermatology Life Quality Index;
CDLQI, Children’s Dermatology Life Quality Index.
QoL, quality of life
IGA, investigator’s global assessment
IL, interleukin
mAb, monoclonal antibody
Ig, immunoglobulin

Outline - AAAAI/ACAAI JTF 2023 Atopic Dermatitis Guidelines

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See the **Appendix** for additional details and practical considerations

Executive Summary - AAAAI/ACAAI JTF 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 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 policy makers.

What's new and different

This JTFPP guideline represents an evolution in trustworthy allergy guidelines[1] and is distinguished from other guidelines[2, 3] through systematic reviews of the evidence with multidisciplinary panelist engagement, adherence to a rigorous guideline development processes, robust use of GRADE that fulfil 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, 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 **Appendix** supplement 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 guideline focused on 5 main questions addressing therapy. Over 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 guideline.

Some of the important changes in this updated practice parameter include:

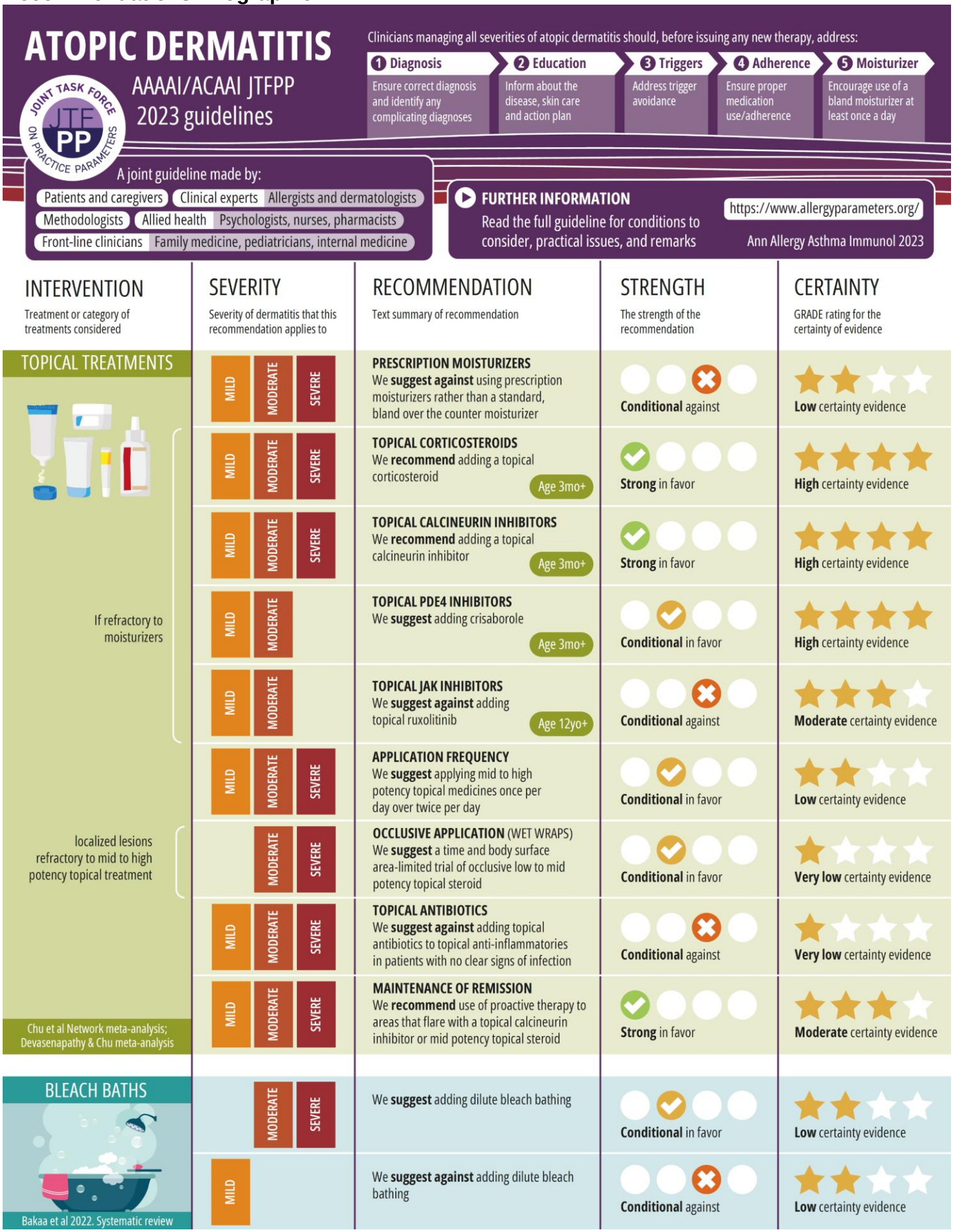
- Guidance on shared decision-making and factors to consider for each recommendation.
- Recommends the usage of topical corticosteroids or topical calcineurin inhibitors in patients with uncontrolled AD in spite of moisturizers
- Highlights the safety of the topical calcineurin inhibitors with typical usage once or twice daily
- Consideration for once daily dosing of topical medications
- Suggests the usage of crisaborole 2% ointment for mild to moderate atopic dermatitis
- Suggests against the use of topical antibiotics for AD alone with no infection
- Recommends proactive therapy with TCS or TCI for patients with a relapsing course
- Suggests bleach baths for AD patients with moderate to severe disease as an additive therapy; suggests against for mild AD
- Suggests against elimination diets for AD
- Suggests consideration of allergen immunotherapy for moderate to severe AD

- Recommends dupilumab for patients 6 months of age or older with moderate-severe AD refractory, intolerant, or unable to use mid-potency topical treatment or tralokinumab for similar patients ages 12 years and older
- Suggests use of oral JAK inhibitors after careful consideration of risks and benefits in adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid to high potency topical treatment and biologics
- Suggests against baricitinib 1 mg, azathioprine, methotrexate, mycophenylate mofetil
- Suggests consideration of cyclosporin 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 **Appendix** 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 five important questions for the management of atopic dermatitis. Answering these 5 questions provides an excellent framework for managing atopic dermatitis. **The infographic** summarizes the recommendations in a format that is easily scalable and shareable, in its unmodified entirety, via social media, flyers, print (eg. two pages side-by-side or a single double-sided page), and as posters (eg. posted in clinician offices). To start, the guideline provides a Good Practice Statement for care of atopic dermatitis.

Recommendations Infographic



ATOPIC DERMATITIS

AAAAI/ACAAI JTFPP 2023 Guidelines

INTERVENTION	SEVERITY	RECOMMENDATION	STRENGTH	CERTAINTY
ELIMINATION DIETS  Oykhman et al Systematic review	MILD MODERATE SEVERE	We **suggest against** the use of elimination diets	**Conditional** against	**Low** certainty evidence
ALLERGEN IMMUNOTHERAPY  Yepes-Nuñez & Chu et al Systematic review	MODERATE SEVERE	We **suggest** adding allergen immunotherapy If refractory, intolerant, or unable to use mid potency topical treatments	**Conditional** in favor	**Moderate** certainty evidence
	MILD	We **suggest against** adding allergen immunotherapy See conditions to consider, e.g. comorbidities, values and preferences	**Conditional** against	**Moderate** certainty evidence
SYSTEMIC TREATMENTS Consider if refractory, intolerant, or unable to use mid to high potency topical treatment 	MODERATE SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **DUPILUMAB** We **recommend** adding dupilumab Age 6mo+	**Strong** in favor	**High** certainty evidence
	MODERATE SEVERE	BIOLOGICS / MONOCLONAL ANTIBODIES **TRALOKINUMAB** We **recommend** adding tralokinumab Age 12yo+	**Strong** in favor	**High** certainty evidence
	MODERATE SEVERE	**UVB TREATMENT** We **suggest** adding clinic-based narrow band UVB treatment	**Conditional** in favor	**Low** certainty evidence
Consider if refractory, intolerant, or unable to use mid to high potency topical treatment and other systemic treatment (inclusive of a biologic recommended above) See conditions to consider, e.g. comorbidities, risk factors, values and preferences, and exceptional circumstances	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **ABROCITINIB, BARICITINIB, OR UPADACITINIB** We **suggest** adding one of these three JAK inhibitors Age varies: 12 or 18 yo+ Suggested daily doses: Abrocitnib 100-200 mg; Baricitinb 2-4 mg; Upadacitinib 15-30 mg	**Conditional** in favor	**Low** certainty evidence
	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **BARICITINIB 1 mg DAILY** We **recommend against** adding baricitinib 1 mg daily	**Strong** against	**Low** certainty evidence
	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **AZATHIOPRINE** We **suggest against** adding azathioprine	**Conditional** against	**Low** certainty evidence
	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **CYCLOSPORINE** We **suggest** adding cyclosporine Shared-decision making should determine whether to start therapy at high dose (5mg/kg) or low dose (3 mg/kg)	**Conditional** in favor	**Low** certainty evidence
	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **METHOTREXATE** We **suggest against** adding methotrexate	**Conditional** against	**Low** certainty evidence
	MODERATE SEVERE	SMALL MOLECULE IMMUNOSUPPRESSANTS **MYCOPHENOLATE** We **suggest against** adding mycophenolate	**Conditional** against	**Low** certainty evidence
Chu et al Network meta-analysis	MILD MODERATE SEVERE	**SYSTEMIC CORTICOSTEROIDS** We **suggest against** systemic corticosteroids for all patients with atopic dermatitis	**Conditional** against	**Low** certainty evidence

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 and an action plan,
(3) address trigger avoidance
(4) ensure proper medication use/adherence
(5) encourage application of a bland moisturizer titrated to symptomatic benefit (at least once, often multiple times, per day).

TOPICAL THERAPIES

Moisturizers are critical for atopic dermatitis care and several prescription moisturizers have become available over the last several years. Based upon the available evidence, the panel suggested against the use of prescription moisturizers (formally marketed as prescription medical devices). Given the close balance versus 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 (TCS, also called topical steroids) are the mainstay of therapy for atopic dermatitis. In patients with uncontrolled atopic dermatitis refractory to moisturization alone, the JTF panel recommends addition of a topical corticosteroid with high certainty evidence of evidence. TCS, used in RCTs mostly for 2-6 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 (class 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 cases. Continuous and prolonged usage of lower 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, 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") topical corticosteroids are also strongly recommended for continued intermittent therapy to prevent future flares ("keeping control" or "proactive therapy").

Topical calcineurin inhibitors are important topical therapies for atopic dermatitis. 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 or tacrolimus) with high certainty evidence. 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 animal data exposed to supraphysiologic doses of systemic calcineurin inhibitors, extrapolation from systemic usage among patients after organ transplant, and data from uncontrolled voluntary reporting systems led the 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 (over 3.4 million patients followed for up to 10 years), and incorporating patient values and preferences, showed no credible increase in cancer with a broad range of typical TCI usage among infants, children, and adults (4.56 per 1000 incidence across all ages

without TCIs versus 4.70 per 1000 with TCIs)[14]. Minor harms of TCIs include local irritation/burning.

The JTF panel also addressed once daily vs. two or more times per day application of topical corticosteroids or topical calcineurin inhibitors and suggests applying the medication once per day over twice per day. 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 bleach baths may help atopic dermatitis. The linked systematic review and meta-analysis synthesizing 10 RCTs[15] showed that the probability to improve AD severity by 50% with adjunctive dilute bleach bathing was 32% versus 22% in the control group (moderate certainty). Little to no difference in adverse events were seen with mild events consisting of dry skin and irritation noted. Changes in other patient-important outcomes (e.g., 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 dilute bleach bathing may be beneficial in patients with moderate and severe atopic dermatitis. Written instructions will be needed to ensure patients use the correct type and concentration of bleach (see **Appendix** 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 severe atopic dermatitis have a higher risk for food allergies than those without AD. Food allergy testing and elimination diets are often considered in an effort to inform how to improve AD control. Recent evidence, however, suggests that oral tolerance to food allergens is promoted through frequent, and perhaps high-dose, oral exposure. Avoidance of food allergens may therefore lead to 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[16]. Compared with no dietary elimination, low-certainty evidence showed that dietary elimination may slightly improve AD severity (50% with vs 41% without dietary elimination improved by a minimally important difference, risk difference of 9% [95% CI, 0-17]), pruritus (daytime itch score [range, 0-3] mean difference, -0.21 [95% CI, -0.57 to 0.15]), and sleeplessness (sleeplessness score [range, 0-3] mean difference, -0.47 [95% CI, -0.80 to -0.13]). Bayesian sensitivity analyses showed 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 to an unrestricted diet. Between both the uncertain benefits and uncertain harms[16], 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 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 allergen immunotherapy could be effective for atopic dermatitis. This guideline update's linked systemic review of 23 RCTs (10 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)[17]. The majority of the studies desensitized patients to house dust mites (HDM;

Dermatophagoides pteronyssinus and/or *Dermatophagoides farinae*), whereas 4 included other inhaled allergens (e.g. pollens). Patients were mostly on standard topical therapy including topical corticosteroids and moisturizers with AIT added on. The majority of the studies included poly-sensitized subjects in addition to HDM sensitization. Based on a combination of clinician-reported AD severity (e.g. SCORAD), AIT likely improved AD severity by 50% or more from baseline compared to 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 i.e. 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 about 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 atopic dermatitis especially if the patient had other allergic diseases that would respond to AIT. The panel noted that 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

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 ultraviolet light therapy (phototherapy).

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 showed that compared to continued standard topical treatment alone, adding dupilumab or tralokinumab led to improvements in multiple patient-important outcomes including AD severity, judged either by patients or clinicians, itch, sleep disturbance, without an increase in serious adverse events or adverse events leading to discontinuation. Conjunctivitis, however, was higher with dupilumab or tralokinumab in comparison to placebo. The linked systematic review of patient values and preferences for treatment of AD[18] along with direct patient and caregiver input showed 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 to dupilumab, tralokinumab was one category lower in efficacy across multiple patient-important outcomes. Tralokinumab is approved for atopic dermatitis in ages 12 years and older. Dupilumab is approved for children/adults age 6 months and older for atopic dermatitis as well as for asthma (ages 6 years and older), eosinophilic esophagitis (ages 12 years and older) and for adults with chronic rhinosinusitis with nasal polyposis and prurigo nodularis. Patients/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 network meta-analysis showed 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. While mild and common harms (e.g. acne, urinary tract infection, upper respiratory 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, while serious infections such as herpetic infections (e.g. eczema herpeticum, herpes zoster) were consistently increased in patients with AD using all 3 studied oral JAK inhibitors, there were no deaths,

cancer, or thrombosis detected in the short studies done. The FDA placed a black box 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, as well as class-wide theoretical safety concerns and boxed warnings for JAK-inhibitors from the US Food and Drug Administration. Oral JAK inhibitors are contraindicated in pregnancy and breastfeeding. 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. JAK inhibitors are immunosuppressants and therefore screening for conditions before use (e.g. 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 above. There are thus multiple implementation considerations, detailed in the **Appendix**, including drug-drug interactions, laboratory and clinical monitoring, FDA approved doses, and practical considerations.

The AAAAI/ACAAI JTF 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 atopic dermatitis (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 policy makers.

Scope of Atopic Dermatitis

AD spans nations, age groups, ethnicities, and cultures[19]. To provide context to the guideline recommendations, we briefly review the scope of the health problem, pathophysiologic 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 affects approximately 13% of children and 7% of adults[20-23]. AD usually develops in early infancy, with 45% of patients developing symptoms by six months of age, 60% by 12 months[1], and approximately 85% by five years[1,2]. Approximately 70% may have spontaneous remission before adolescence, while 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[24].

Among a number of diagnostic approaches for AD[25-27], Hanifin and Rajka[28] diagnostic criteria and the UK working party[29] modifications are the most widely validated and used for diagnosis (**Table 1**), but a consensus reference standard does not exist[25, 26, 30, 31]. There are over 180 different ways to classify AD[32].

Hanifin and Rajka[28]		**UKWP 1994[29]**	
3+ of 4:	Pruritus	An itchy skin condition (or parental report of scratching or rubbing in a child)	
	Typical morphology and distribution	3+ of 5:	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).
	Chronic or chronically relapsing dermatitis		Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4).
	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).
and 3+ of 23:	Xerosis		History of a general dry skin in the last year.
	Icthyosis/palmar hyperlinearity/keratosis pilaris		Onset under the age of 2 (not used if child is under 4).
	Immediate (type I) skin test reactivity		
	Elevated serum IgE		
	Early age of onset		
	Tendency toward cutaneous infections (e.g. 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 subscapular 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	

AD symptoms, associated sleep disturbance, and atopic and non-atopic comorbidities contribute to patient and caregiver burden. AD negatively affects quality of life and activities of daily living with similar or worse impact compared to other chronic skin and systemic diseases[33, 34].

Intense pruritus occurs in most patients with AD, is difficult to control, and is commonly reported as the most burdensome symptom of disease[23, 35, 36]. Over 85% of patients with moderate to severe AD report daily itch and 42% experience itch for 18 or more hours each day[37]. Over 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[38, 39].

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[40, 41]. Subjective sleep problems include difficulty falling asleep, frequent nighttime wakening and, compared with controls, excessive daytime sleepiness[41]. Objective findings include prolonged sleep onset latency, reduced sleep efficiency and increased time awake[41]. Sleep disturbance is likely driven by itching and scratching which is more difficult to suppress at night[42].

Due to AD, patients commonly report activity limitations and self-consciousness about the appearance of their skin, leading to avoidance of social interactions[23, 43]. 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[44-47].

Pathophysiology and mechanisms overview

The pathogenesis of AD is complex and multifactorial[48-50] and is reflected in heterogeneous clinical phenotypes[32]. Detailed reviews of AD pathophysiology appear elsewhere[48, 51, 52]. 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 [e.g. claudin-1]) predispose to increased transepidermal water loss and cutaneous dryness in AD[53, 54]. 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[55], leading to an activation of Th2 cells. New systemic therapies that specifically target these cytokines demonstrate 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 Th17/22 and Th1 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 predisposes patients to increased skin infections, predominantly due to *S. aureus* and viruses (e.g. herpes simplex viruses, *molluscum contagiosum virus*)[56]. While 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[57]. In addition, there is growing interest in understanding the 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 non-atopic (depression, anxiety, neurocognitive impairment, skin infections, and adverse effects of treatment) health problems occur in patients with AD[58-62]. AD severity is associated with developing such comorbidities and may be due to uncontrolled disease, systemic inflammation, and disturbed sleep[63-65]. Complications of skin traumatization in AD include bacteria, 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[66-68]. Conjunctivitis, for example, can occur after treatment with dupilumab, tralokinumab, or lebrikizumab.

AD is associated with increased fracture incidence[69, 70] which may be due to decreased physical activity, increased systemic inflammation, and excessive use of certain treatments such as potent topical and systemic corticosteroids[71, 72]. Shared mechanisms may also promote AD's possible association with cardiovascular and metabolic diseases, including obesity, hypertension, myocardial infarction, stroke, and heart failure[73-75].

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 healthcare 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[44, 47, 76]. Out-of-pocket expenses are particularly important to patients and families and can affect management outcomes[76]. Recent survey data from the National Eczema Association indicates the median annual AD out-of-pocket expense was $600; 42% of AD patients reported greater than $1000 out-of-pocket annually, and 9% reported out-of-pocket greater than $5,000 per year. Higher out-of-pocket expenses are associated with increased disease severity and flares[76, 77].

These data also indicate that many AD patients use, including concurrently, at least 3 prescription therapies[77]. 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[45]. Caregivers consequently face trade-offs such as working less, working flexible hours, or leaving the workforce, to accommodate the time-intensive demands of managing AD[44, 45]. Disparities in social determinants of health exacerbate these burdens[78].

Collectively, these data indicate that there are potentially large financial and non-financial 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 many other regions of the world[79, 80], race, ethnicity, and ancestry are terms that are often confused and used incorrectly[81] in medicine and research. Historically racialized communities continue to face health disparities due to a number of factors including structural and systemic racism[82-85]. 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[86] and extensor surface, eyelid, and inverse flexural involvement (see https://eczemainskinofcolor.org/ and https://nationaleczema.org/eczema-skin-of-color/)[5, 87, 88]. 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[89, 90]. Consistent with calls to improve representation of diverse ethnic backgrounds and skin tones in medicine[91-95] and society, we define erythema to include transient skin alterations characteristic of active AD inflammation including red, shades of brown, violaceous, or grey appearances. Post-inflammatory 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, while there is interest in understanding potential variation in the AD inflammatory response across race, ethnicity, or ancestry[96, 97], 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 impact patient and family diagnosis and optimal health care access and utilization[98].

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 versus patients identified as white, 6.7 [95%CI 4.8-9.5])[99], and patients identified as Black or African American accounted for 20% (adjusted odds ratio, 3.4 [95%CI 2.5-4.7]). Indigenous Peoples were excluded from the analysis. Further, historically racialized groups face worse outcomes and inequities in access to care[100]. For example, children with AD in the US identifying as Black or Hispanic are more likely to miss school[101] and, rather than access specialist care, use primary care and the emergency department for AD[102]. Historically racialized groups are also less likely to receive evidence-based treatments appropriate for their AD severity[103]. 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[104-107]. Optimally addressing the racial, ethnic, and cultural diversity of Indigenous peoples requires not only actively and equitably engaging them in research and policy-making, but also incorporating culturally-sensitive (e.g., appreciating Indigenous Ways of Knowing[108] and research practices[109]) decision-making during individual clinical encounters[110].

Given the complex factors driving disparities, improved research and educational initiatives alongside interdisciplinary and multi-stakeholder 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 accounting for patient contextual factors in shared decision-making[82, 84, 111, 112]. Clinicians should also promote structural and organizational change[113]. 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 Joint Task Force (JTF) on Practice Parameters (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 policy makers 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 (Grading of Recommendations Assessment, Development and Evaluation) approach[4, 7, 114, 115], Guidelines International Network-McMaster[116], RIGHT[117], AGREE II[118], Institute of Medicine[1, 119], and in compliance with the AAAAI/ACAAI JTFPP policies. We fulfilled criteria required to report robust use of GRADE[4]. The **Appendix** 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 (via a JTFPP Liaison: MG), including document review, feedback, and approval of the guideline. The guideline panel, striving for equity, diversity, and inclusiveness (e.g., age, gender, race and 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 front-line clinicians (family practice, pediatrics, internal medicine, pharmacist), and four 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 (GG) assisted the Methods Chair, and observers (AWLC, IXZ, LC, PO, LB) from the Evidence in Allergy Group attended the panel meetings but did not directly participate in discussions. 22 additional healthcare workers (e.g., nurses, pharmacists, infectious disease specialists), patient and caregiver partners, and patient advocacy group representatives 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, screen 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 JTFPP via the AAAAI and ACAAI, non-profit 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)[119] and the Guidelines International Network[120]. 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 **Appendix** provides the completed "Disclosure of Interest" forms of all panel members. The **Appendix** also summarizes decisions about which interests were judged to be conflicts. At the time of appointment, a majority of the guideline panel, including the co-chairs, had no conflicts of interest as defined and judged by JTFPP (i.e., 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, the majority 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. While 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 (non-financial) 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 healthcare 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 via 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 four 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[121], the Harmonizing Outcomes Measures for Eczema (HOME)[35, 36, 122] 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[18]. 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[123] led by the Evidence in Allergy Group. These included:

1. Systematic review and meta-analysis of bleach baths vs. usual baths for atopic dermatitis[15]
2. Systematic review and meta-analysis of dietary elimination vs. usual diet for atopic dermatitis[16]
3. Systematic review and meta-analysis of allergen immunotherapy versus no allergen immunotherapy for atopic dermatitis[17]
4. Systematic review and meta-analysis of cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis[14]
5. Systematic review and network meta-analysis of topical treatments for atopic dermatitis – Submitted and referred to here as [the topicals NMA]
6. Systematic review and network meta-analysis of systemic treatments (monoclonal antibodies, small molecules [e.g. JAK inhibitors, cyclosporine, methotrexate), ultraviolet light therapy) for atopic dermatitis – Submitted and referred to here as [the systemics NMA]
7. Systematic review of values and preferences of patients and caregivers regarding treatment of atopic dermatitis[18]

While 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:

8. What Parents Should Know About Atopic Dermatitis JAMA Pediatrics Patient Page[5] (1-page handout)
9. 5 things to know about managing infant atopic dermatitis[6] (1-page handout)
10. 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, 124]. 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, precision, consistency and magnitude of the estimates of effects, directness 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[123] we additionally considered intransitivity[125] and incoherence[123]. Details of the GRADE approach, including definition of terms, are summarized elsewhere[7, 123, 126]. 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 six 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.

Document Review

All members of the panel reviewed draft recommendations, revised, and then made them available online on *[date]* for external review by stakeholders, including allied organizations, other medical professionals, patients, and the public. *[Number]* individuals or organizations submitted comments in addition to [xx] journal peer-reviewers. In response to pertinent comments, the panel accordingly revised the document, but no changes were made to the recommendations. On *[date]*, 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…") and has the following interpretation (**Table 2**):

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.	The majority of 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.
Policy makers	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.	Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess if decision-making is appropriate.
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An

	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.	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.

The **Infographic** summarizes the recommendations.

How to use these guidelines

JTFPP guidelines are primarily intended to help clinicians work with patients to make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy, and to state future research needs. They may also be used by patients independently of their 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, as well as 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 interactive forthcoming decision aids. 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.

JTF AAAAI/ACAAI Atopic Dermatitis (Eczema) Management Recommendations

The **Infographic** 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, (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 (e.g. scabies), and local and systemic infections (e.g., *Streptococcal*, *Staphylococcal*, fungal, syphilis). 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 re-appraising the large body of literature addressing moisturizers to inform this good practice statement. A 2017 systematic review of 77 randomized clinical trials (RCTs) established that moisturizers overall improve patient-important AD outcomes[127]. Further, published in 2022, a RCT of 555 children with mostly mild AD (baseline mean [SD] POEM of 9 [6] and EASI 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 all 4 groups[128]. Together, these data suggest that the best moisturizer is the one that patients will use regularly, and shared decision-making should express the potential tradeoffs between benefits (e.g., perhaps greater benefit with ointment-based moisturizers for more severe disease) and acceptability. A 2019 narrative review[129], 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[18].

Table 3. Some reported severity strata for measuring atopic dermatitis.

Perspective & Domain	Instrument name/design	Total score range	Number of strata	Mild	Moderate	Severe
Clinician-rated AD Severity	EASI[130]	72	4	0.1-5	6-22	23-72
Clinician-rated AD Severity Patient-rated itch, sleep disturbance	SCORAD[130]	103 (83 AD severity, 10 each for itch and sleep)	4*	10-28	29-48	49-103
Patient-rated AD Severity	POEM[131]	28	5#	3-7	8-16	17-24
Patient-rated Itch	VAS or NRS[132]	10	3	0-3	4-6	7-10
Patient-rated Sleep disturbance	VAS or NRS**	10	3**	0-3	4-6	7-10

Patient-rated AD-related quality of life	DLQI[132] CDLQI[133]	30	3[##]	0-5	6-10	11-30

Table 3 footnotes: Strata should not be rigidly interpreted as they reflect continuums of severity[134]; 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[97]). Values lower or higher than the bands strata here represent either less severe or "clear" skin, or, vice versa, "very severe" activity. EASI, Eczema Area and Severity Index, measures signs of erythema/redness, induration/thickness, excoriation/scratching, lichenification; SCORAD, SCORing Atopic Dermatitis, measures similar domains as EASI and in addition, oozing/crusting, dryness, and patient-reported sleep loss, and itch; POEM, Patient-Oriented Eczema Measure, measures over the past 7 days, patient-reported itch, sleep disturbance, bleeding, weeping/oozing, cracks/fissures, flaking, dryness/roughness; VAS, visual analogue scale; NRS, numeric rating scale; DLQI, Dermatology Life Quality Index; CDLQI, Children's Dermatology Life Quality Index.

*Kunz et al original paper describes 3 strata for SCORAD[135]

0-24 = mild
25-49 = moderate
50-103 = severe

[#]Vakharia 2017 et al reported 3 strata for POEM[132]

0-7 = mild
8-16 = moderate
17-28 = severe

**No direct data, values taken from itch.

[##]Original DLQI[136], and CDLQI[137] had 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

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[138], and up-to-date written action plans[139] are valued[140, 141], and may improve outcomes[142-145] boost confidence[139]. Digital internet-based tools, as demonstrated in Eczema Care Online's two randomized trials published in 2022[146], hold promise.

TOPICAL TREATMENTS

With AD being an immune-driven disease, patients will require anti-inflammatory treatment. While 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: prescription moisturizers (marketed as medical devices), topical corticosteroids (TCS), topical calcineurin inhibitors (TCIs), topical phosphodiesterase 4 inhibitors (PDE4is), topical Janus kinase (JAK) inhibitors, and topical antibiotics. How the medication is applied can vary by the number of applications per day or whether it is applied under occlusion (e.g., wet wraps). One 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 **Appendix** 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 two phases (**Figure 1**): (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[147]. Another term for regular use of topical treatments to prevent a future flare is proactive therapy.

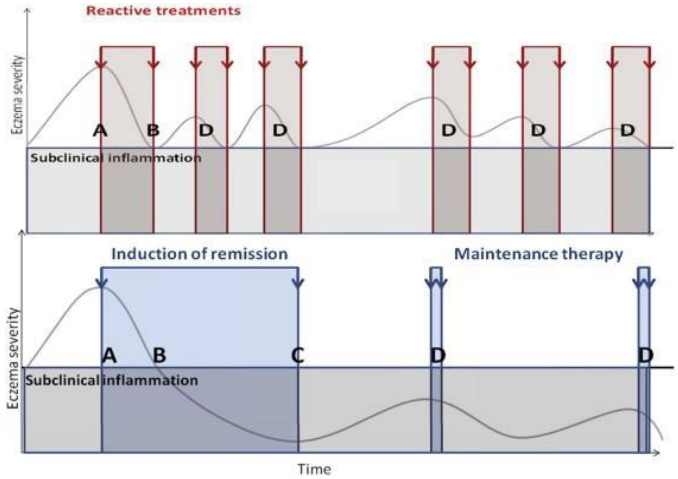


Figure 1. Diagram *(top)* illustrates what might happen when AD treatment ceases once signs and symptoms have superficially reduced (the period from point A to point B) as opposed to what might happen *(bottom)* if initial treatment is extended to clear subclinical disease (point C). Induction of remission 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 J Allergy Clin Immunol. 2014 Jun;133(6):1615-25.e1.[147]

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.

Recommendation 2: In patients with atopic dermatitis, the JTF panel suggests using a standard, bland (free of fragrance and other contact allergens) over-the-counter moisturizer over a prescription moisturizer medical device (e.g. 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 versus 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 network meta-analysis of all topical prescription treatments, including 9 RCTs involving various prescription moisturizers (approximately 400 patients), showed that compared to 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 versus 24% with prescription moisturizer; absolute risk difference [RD] 6% [95%CI -3% to 16%]) and probably slightly improve flares (10% with standard moisturizer versus 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 versus 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[18] along with direct patient and caregiver input on their perspectives on prescription and over-the-counter moisturizers showed that many patients with AD prefer odorless treatments that are not visible and have a low impact on daily life; that they value non-pharmacologic therapies; and that they also value the texture or sensation of moisturizer on the skin.

Given the close balance between the two 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 (e.g. 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 [e.g. 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 to 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. While 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 100g tube to $1000 or more. (e.g. GoodRx on Jan 1, 2023, lists Epiceram at $6826 retail price for a 90g tube, and Atopiclair $86 retails for a 100g tube; Eletone $306 retails for a 100g tube; Neosalus $177 retails for a 100g tube; PruMyx $137 retails for a 140g 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 to 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 over 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 minority of patients (see conditions to consider) might prefer prescription moisturizers compared to over-the-counter ones. The low certainty evidence and close balance of benefits versus 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 network meta-analysis synthesized 219 RCTs enrolling 43,123 infants, children, and adults with primarily mild-moderate AD addressing 68 different treatments. Figure 2 presents the summary of findings across outcomes. Few studies compared the effects of TCS by location of the body (e.g., head and neck versus rest of body), albeit those that did suggested similar treatment effects across body parts.

TCS, used in RCTs mostly for 2-6 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 out of 3574 RCT children and adult participants applying mild, moderate, and potent TCS for primarily either 1-6 weeks or 16-20 weeks (raw proportion: 7 per 1000 (95%CI 5 to 11 per 1000])[148].

Values and preferences: The linked systematic review[18] along with direct patient and caregiver input showed that patients with AD prefer to use non-prescription therapies before TCS, use TCS for the 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 TCS 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 network meta-analysis (submitted topicals NMA) showed 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 (**Figure 2**). Hence, both systems must be known in order 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 (class 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 cases. Continuous and prolonged usage 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 **Appendix** 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").

	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	-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							
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)	
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)
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 Moisturizer	-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)

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 different from standard care	Possibly not different from standard care

Figure 2. Summary of comparative effects of topical interventions on patient-important outcomes for controlling atopic dermatitis.
The certainty of the evidence was rated by the Grading of Recommendations Assessment, Development and Evaluation 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 analysed interventions are presented in the associated systematic review (submitted). MD = mean difference. RD = risk difference. CrI = credible interval.

Comparison of representative topical corticosteroid preparations (classified according to the United States system)				
US 7 class Potency group*	**Corticosteroid**	**Vehicle type/form**	**Brand names (United States)**	**Available strength(s), % (except as noted)**
Super-high potency (group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05
	Diflucortolone valerate (not available in United States)	Ointment, oily cream	Nerisone Forte (United Kingdom, others)	0.3
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (group 2)	Amcinonide	Ointment	Cyclocort¶, Amcort¶	0.1
	Betamethasone dipropionate	Ointment	Diprosone¶	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon¶, Florone¶	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex¶	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (group 3)	Amcinonide	Cream	Cyclocort¶, Amcort¶	0.1
		Lotion	Amcort¶	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone¶	0.05
	Betamethasone valerate	Ointment	Valisone¶	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream	Topicort LP¶	0.05
	Diflorasone diacetate	Cream	Florone¶	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar¶	0.025
	Flurandrenolide	Ointment	Cordran	0.05
	Hydrocortisone valerate	Ointment	Westcort	0.2
	Mometasone furoate	Cream, lotion, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1
		Ointment	Kenalog¶	0.1
		Ointment	Trianex	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralone	0.1
Lower-mid potency (group 5)	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val, Valisone¶	0.1
	Desonide	Ointment	DesOwen, Tridesilon¶	0.05
		Gel	Desonate	0.05
	Fluocinolone acetonide	Cream	Synalar¶	0.025
	Flurandrenolide	Cream, lotion	Cordran	0.05
	Fluticasone propionate	Cream, lotion	Cutivate	0.05

	Hydrocortisone butyrate	Cream, lotion, ointment, solution	Locoid, Locoid Lipocream	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1
	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon¶	0.05
		Lotion	DesOwen, LoKara	0.05
		Foam	Verdeso	0.05
	Fluocinolone acetonide	Cream, solution	Synalar¶	0.01
		Shampoo	Capex	0.01
		OilΔ	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (group 7)	Hydrocortisone (base, ≥2%)	Cream, ointment	Hytone, Nutracort¶	2.5
		Lotion	Hytone, Ala Scalp, Scalacort	2
		Solution	Texacort	2.5
	Hydrocortisone (base, <2%)	Ointment	Cortaid, Cortizone 10, Hytone, Nutracort	1
		Cream	Cortaid¶, Cortizone 10, Hytone, Synacort	1
		Gel	Cortizone 10	1
		Lotion	Aquanil HC, Sarnol-HC, Cortizone 10	1
		Spray	Cortaid	1
		Solution	Cortaid, Noble, Scalp Relief	1
		Cream, ointment	Cortaid	0.5
	Hydrocortisone acetate	Cream	MiCort-HC	2.5
		Lotion	Nucort	2

* Listed by potency according to the United States classification system: group 1 is the most potent, group 7 is the least potent. Other countries use a different classification system with reverse ordering and/or fewer groupings.

¶ Inactive United States brand name for specific product; brand may be available outside United States. This product may be available generically in the United States.

Δ 48% refined peanut oil.

2. Tadicherla S, Ross K, Shenefelt D. Topical corticosteroids in dermatology. Journal of Drugs in Dermatology 2009; 12:1093.

3. U.S. Food & Drug Administration Approved Drug Products with Therapeutic Equivalence (Orange Book). Available at: https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm (Accessed on June 18, 2017).

Table 4. Comparison of representative topical corticosteroid preparations (classified according to the United States system, adapted from UpToDate). The linked systematic review and network meta-analysis (**Figure 2**) shows 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.

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

Topical calcineurin inhibitors (topical pimecrolimus and tacrolimus)

Recommendation 4: In patients aged 3 months or older with uncontrolled atopic dermatitis refractory 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).

Benefits and harms: **Figure 2** summarizes the effects of topical calcineurin inhibitors for AD, including:

- 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 to using either TCS or TCI alone (low certainty).
- Few studies compared the effects of TCIs by location of the body (e.g., head and neck versus rest of body), albeit those that did suggested similar treatment effects across body parts.

Select review of animal data exposed to supraphysiologic doses of systemic calcineurin inhibitors, extrapolation from systemic usage among patients after organ transplant, and data from uncontrolled voluntary reporting systems led the FDA to add a boxed warning[149] 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, showed no credible increase in cancer with a broad range of typical TCI usage among infants, children, and adults (4.56 per 1000 incidence across all ages without TCIs versus 4.70 per 1000 with TCIs)[14]. Minor harms of TCIs include local irritation/burning.

While the panel has individually recommended TCS and TCI versus no added anti-inflammatory, the combination of TCS with TCI has low certainty for modest added benefits over using either agent alone and the panel may address this 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. Tacrolimus 0.03% is approved for ages two years and older. 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 showed that positive framing, e.g., a "cooling sensation and that this is a sign the medication is working" may increase acceptability of topical medications for AD over 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 counselling 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])[150]. 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. While 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 to TCI (e.g., 454g tubs versus 100g 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 **Appendix** provides additional practical information and implementation considerations in 1-2 page handouts.

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	15g	$ 9.68	$ 4.97	454g cream jar ($18.66 for ointment)	$ 35.79	$ 13.39
Triamcinolone Acetonide	0.50%	Triderm	Cream	15g	$ 11.89	$ 6.27	454g jar	$ 40.85	$ 14.30
Triamcinolone Acetonide	0.50%	Kenalog	Ointment	15g	$ 16.78	$ 7.66	60mL lotion (0.1% or 0.025%)	NA	NA
Betamethasone Dipropionate Augmented	0.05%	Diprolene augmented	Cream	15g	$ 23.64	$ 5.03	50g	NA	$ 6.80
Betamethasone Dipropionate Augmented	0.05%	Diprolene augmented	Ointment	15g	$ 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	15g	$ 33.32	$ 7.63	45g	$ 74.72	$ 18.50
Mometasone Furoate	0.10%	Elocon	Cream	45g	$ 50.19	$ 12.15	45g ointment	$ 50.45	$ 11.41
Mupirocin	2%	Bactroban	Ointment	22g	$ 51.56	$ 5.25	NA	NA	NA
Fluocinonide	0.05%	Lidex	Cream	30g	$ 53.42	$ 16.29	60mL solution, or 60g ointment	NA	NA
Fluticasone Propionate	0.05%	Cutivate	Cream	60g	$ 55.80	$ 14.94	NA	NA	NA
Triamcinolone Acetonide	0.10%	Oralone	Paste	5g	$ 72.04	$ 18.78	NA	NA	NA
Clobetasol Propionate	0.05%	Temovate	Cream	15g	$ 78.33	$ 4.78	Foam, lotion, gel, ointment (max 60 g; 118mL)	$ 90.81 to 365.30	$ 14.69 to 50.97
Hydrocortisone Valerate	0.20%	Westcort	Cream	15g	$ 83.45	$ 7.02	NA	NA	NA
Fluocinolone Acetonide Body	0.01%	Derma-smoothe/FS Body	Oil	118.28mL	$ 103.99	$ 24.85	NA	NA	NA
Halobetasol Propionate	0.05%	Ultravate	Cream	50g	$ 169.75	$ 26.59	50g ointment	$ 200.50	$ 30.57
Tacrolimus	0.10%	Protopic	Ointment	30g	$ 182.67	$ 35.20	100g	$ 676.45	$ 71.34
Clobetasol Propionate Emollient	0.05%	Temovate E	Cream	60g	$ 219.99	$ 23.18	NA	NA	NA

Table 5. Example of some available topical treatment sizes and costs in USA (Cost Plus Drugs April 2023). Additional examples, including additional TCIs and crisaborole, are available from The Medical Letter on Drugs and Therapeutics and reflect wholesale acquisition costs in 2020[151, 152]. As of April 2023, the GoodRx price for a 60g tube of ruxolitinib cream costs $2410 at Walgreens. 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.

Topical corticosteroids under occlusion (wet wraps) vs standard non-occlusive application

Temporarily applying TCS under occlusion is another method of treating localized recalcitrant lesions and is often referred to as wet wrap therapy since wet (damp) clothing or dressings are used to occlude the applied TCS[11, 153].

Recommendation 5: In patients with localized uncontrolled atopic dermatitis refractory to mid-high potency topical treatment (US class 2-5 or tacrolimus), the JTF panel suggests addition of a time and body area-limited (e.g. 4-7 days; minimum 1 hour to maximum overnight, once per day) trial of occlusive low-mid potency topical corticosteroid (US class 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 (submitted topicals NMA). 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: Whereas 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 **Appendix**.

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 over the minor burdens and uncertain minor harms, compared to standard non-occlusive application.

Implementation considerations: If wrapping overnight, ensure the wrap is not constrictive. Publications[153, 154] and online educational resources[155] (e.g. 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 **Appendix** provides additional practical information and implementation considerations in 1-2 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 class 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 over 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 over once per day application.
3. Patients who value a twice per day skin care routine, or who respond better to twice per day use, over once per day, may prefer the twice daily application.

Benefits and harms: 9 RCTs comprising 1507 participants evaluated twice per day application of TCS (US class 1-5) or tacrolimus compared to once per day. They provided high certainty evidence for a small difference between regimens (mean difference [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 to 9 more]). This is just above the a priori threshold of 3 per 100 set by the guideline panel. Twice per day application, compared to 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 (submitted topicals NMA).

Values and preferences: The systematic review of values and preferences[18] 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 to 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 over 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 (e.g. when facing more severe flares) drove the conditional recommendation.

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

Topical PDE4 inhibitors

While many topical PDE4 inhibitors are in development, 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 to crisaborole.
2. The severity of AD - the small benefits shown 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 non-corticosteroid 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 network meta-analysis, including 5 randomized trials and more than 2000 participants (including two trials comparing crisaborole to either TCS 5 or pimecrolimus), addressing crisaborole showed 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 (**Figure 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 to standard care with a moisturizer alone, would align with patient values and preference for alternative non-corticosteroid 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 over 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[150]. 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. While the panel did not yet render an official recommendation for TCS or TCI versus crisaborole, many clinical experts and patients will start with TCS or TCI first. Future updates to the guideline may address this. The **Appendix** provides additional practical information and implementation considerations in 1-2 page handouts.

Topical JAK inhibitors

While 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 atopic dermatitis.

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 that place a higher value on certain larger benefits and safety profile of other topical treatments (e.g. 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, may prefer other treatments compared to topical ruxolitinib.
3. Patients that have not responded to other topical therapies and/or those that 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 network meta-analysis, including 3 RCTs and over 1400 adolescent and adult participants with mild AD (mean 9.5% body surface area involvement) comparing, after a run-in period, topical ruxolitinib versus either standard care or TCS 4 (triamcinolone 0.1% cream), showed high or moderate certainty improvements in AD severity (RD 23 more per 100 [6 to 41 more]), itch (34 more per 100 [20 to 47 more]), sleep disturbance (4 more per 100 [0 to 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. Topical ruxolitinib is similar in efficacy in improving patient-important AD outcomes to pimecrolimus (between TCS 5 and TCS 6/7) (**Figure 3**) (submitted topicals NMA).

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 [with risks] to credibly estimate the effect on death, cancer, thrombosis or serious infections. Stroke was observed in the ruxolitinib group in the TRuE-AD trials, but recent data, a mix of observational and randomized data, to 40 weeks suggest favorable safety[156]. The FDA has placed a black box warning label on all JAK inhibitors due to a recent study in rheumatoid arthritis and an oral pan-JAK inhibitor, tofacitinib. The ORAL

surveillance study was a 40-month, 4362 participant study comparing tofacitinib to a TNF inhibitor in patients with rheumatoid arthritis aged 50 years or older, also taking methotrexate, and at least one risk factor for cardiovascular disease. Compared to TNF inhibitors, tofacitinib increased major cardiovascular adverse events (2.5% vs 3.4%; 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%). In contrast to TCIs for AD, systemic absorption routinely occurs with topical JAK inhibitors (with studies of ruxolitinib suggesting limiting application to less than 20% BSA and discontinuous use as potential strategies to mitigate this)[157-159]. 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 (e.g. using the framework used to evaluate the association with TCI[14]), 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[18] and direct input from patient partners showed 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 is another potential resource limitation[160]. 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 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 to standard care, and in particular, when considering other treatments with higher certainty for safety.

Implementation considerations: 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 non-immunocompromised nor immunosuppressed patients, and (3) in a short-term or non-continuous 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. While the panel did not yet render an official recommendation for TCS or TCI versus ruxolitinib, many clinical experts and patients will start with TCS or TCI first. Similarly, clinical experts expressed that although might not be first line for most patients, ruxotitinib might still be a good resource for those patients for whom TCS and TCI do not yield sufficient control. The **Appendix**

provides additional practical information and implementation considerations in 1-2 page handouts.

Topical antibiotics vs no addition of topical antibiotics

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

Conditions to consider:

1. Patients with uncontrolled AD and without serious skin infection that place a high value on avoiding polypharmacy and antimicrobial resistance will prefer to avoid adding topical antibiotics to standard care. For severe skin infections (extent or intensity, e.g. accompanied by fever or other systemic symptoms), guidance from the Infectious Disease Society of America addresses when to use systemic or topical antibiotics[161].
2. Patients who are immunocompromised or immunosuppressed, have a more severe (extent or intensity) infection (particularly impetigo or ecthyma[161]), a history of severe infections, severe AD, or that place a high value on avoiding potential complications of bacterial skin infections may prefer adding topical antibiotics 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 (IDSA) is available[161] (e.g. abscesses, furuncles/carbuncles, purulent or necrotizing skin infections, erysipelas, cellulitis, animal bites, other types of skin infections).

Benefits and harms: The topical treatments network meta-analysis showed that the few studies addressing the addition of topical antibiotics in combination with topical corticosteroids or topical calcineurin inhibitors (e.g. fucidin, antibiotics, triclosan) compared to 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. These findings accord with no significant improvement across outcomes seen in RCTs addressing oral antibiotics for AD (either infected[162-164] or uninfected[165-167]) and an increasing conceptual view that host-microbiome interactions in AD are more complex than the simple presence or absence of *Staphylococcus aureus*[168].

Values and preferences: The systematic review of patient values and preferences[18] as well as 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 antibiotics be effective when needed.

Contextual factors: While topical antibiotics are available, their overuse contributes to antimicrobial resistance to individual patients and populations, thereby increasing resource use. 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[169] and United Nations[170].

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 and the large uncertainty for any benefit with adding a topical antibiotic. 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 **Appendix** 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)?

As needed vs routine intermittent use 2-3 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 class 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, 4-12 months in duration, showed that on average, proactive therapy, compared to reactive therapy, reduced the incidence of flare (69 per 100 vs 38 per 100, RD -31 [-40 to -20], Relative risk: 0.55 (CI 95% 0.42 - 0.71)), with little to no adverse effects (24% vs 27%, RD 3 [-2 to 9]). **Figure 4** summarizes the less certain evidence for important differences among various TCS groups and TCIs.

Odds ratio (95% credible interval) *Absolute risk reduction*	**TCS Group 5**	**TCS Group 3**	**Tacrolimus**	**Pimecrolimus**	**Standard Care (Reactive)**
	0.46 (0.22 to 0.97) *-19* *(-36 to -1)*				
	0.33 (0.17 to 0.64) *-27* *(-41 to -11)*	0.73 (0.32 to 1.56) *-8* *(-28 to 10)*			
	0.30 (0.14 to 0.64) *-29* *(-44 to -11)*	0.65 (0.27 to 1.52) *-10* *(-32 to 9)*	0.89 (0.43 to 1.92) *-3* *(-21 to 14)*		
	0.15 (0.09 to 0.24) *-43* *(-50 to -34)*	0.32 (0.17 to 0.60) *-28* *(-41 to -12)*	0.44 (0.28 to 0.71) *-20* *(-31 to -8)*	0.50 (0.27 to 0.90) *-17* *(-32 to -2)*	

GRADE certainty of evidence

High | Moderate | Low | Very Low

Figure 4 from Evidence in Allergy-AAAI/ACAAI JTFPP Topical Treatments for AD network meta-analysis. **League table for maintenance of remission on atopic dermatitis flares.** The league table shows the comparative effects of each intervention in the column compared to the intervention of the row, presented as odds ratios and 95% credible intervals 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 6-12 months in duration, was 63% (57% to 72%).

Values and preferences: The systematic review of patient values and preferences as well as 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 show that it uses less overall topical medication compared to 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 to 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 two consecutive days of per week (e.g. weekends) for several months to maintain AD control. 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 **Appendix** 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, epidermal, 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 upregulates anti-inflammatory pathways and decreases stability of mRNA including collagenase, elastase, chemokines and cytokines.

Topical calcineurin inhibitors (TCI) bind to FK506 binding protein in the cells. The drug suppresses calcineurin activity leading to decreased expression of both Th1 and Th2 cytokines as well as interferon-gamma and tumor necrosis factor-alpha. However, TCI are larger molecules, so they have less systemic absorption.

Topical JAK inhibitors preferentially inhibit one or many JAK molecules depending on the specificity of the drug. Delgocitinib, for instance, is a pan-JAK inhibitor that 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. JAK inhibitors are small molecules, so they have the potential for systemic 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 it be used?

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

Conditions to consider:

1. Whether the bleach bathing 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[15] showed that the probability to improve AD severity by 50% with adjunctive dilute bleach bathing was 32% versus 22% in the control group (moderate certainty). Similar effects were seen in studies enrolling participants with or without a history of skin infections. No differences in effect by age were seen. Patients using dilute bleach baths were likely to see effects in AD severity within 4 weeks of treatment. Dilute bleach bathing compared to usual bathing 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 (e.g., 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[18] and along with direct patient and caregiver input on their perspectives on bleach baths showed that patients valued a non-corticosteroid 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 to 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 to 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, while those presenting with low disease activity such as an EASI of 10 who 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 bathing compared to 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 bathing might improve equity in populations in remote areas that have access to bleach and bathing but are sufficiently remote to make medical visits difficult. Though bleach bathing can be associated with an odor and a routine to become familiar with, the panel inferred this treatment to be acceptable to the majority of well-informed patients. Dilute bleach bathing is as feasible as usual bathing without bleach. The **Appendix** 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 as well as potential harms, however, contributed to the conditional recommendation. Specifically in patients with moderate-severe disease dilute bleach bathing 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 bathing should be adjunctive to standard AD skin care (moisturizing, topical medication use, action plans for flare management) and that considering adjunctive dilute bleach bathing should not detract fundamental skin care routines (see **Good Practice Statement**). The **Appendix** and online resources present additional guidance.

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

Conditions to consider:

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

Benefits and harms: The estimated treatment effect of dilute bleach baths for milder AD (e.g. 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 above, 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 bathing even if their disease activity is mild.

<u>Mechanism of action of dilute bleach bathing</u>

The initial hypothesis for the mechanism of action of dilute bleach baths in AD was that it would have a direct anti-bacterial activity, in particular against the overabundance of *S. aureus*[168, 171]. However, subsequent investigations have demonstrated 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*[172]. Other studies have suggested instead anti-inflammatory, anti-pruritic, 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 to an unrestricted diet (conditional recommendation, low certainty evidence).

Conditions to consider:

1. Young age of patient (e.g. 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: The systematic review and meta-analysis identified 10 RCTs (599 participants) addressing benefits and harms of dietary elimination for AD[16]. Compared with no dietary elimination, low-certainty evidence showed that dietary elimination may slightly improve AD severity (50% with vs 41% without dietary elimination improved by a minimally important difference, risk difference of 9% [95% CI, 0-17]), pruritus (daytime itch score [range, 0-3] mean difference, -0.21 [95% CI, -0.57 to 0.15]), and sleeplessness (sleeplessness score [range, 0-3] mean difference, -0.47 [95% CI, -0.80 to -0.13]). Bayesian sensitivity analyses showed 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 empiric 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 showed 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 point; odds ratio [OR], 1.3; 95% CI, 1.04-1.68 per month[173]). 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[18] along with direct patient and caregiver input on their perspectives on dietary elimination showed that many patients with AD will consider a diet therapy; that they value non-pharmacologic therapies; that they 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[16], the panel inferred that most well-informed patients placed 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 (e.g. 14% higher chance of developing a potentially lifelong food allergy) and burdens compared to uncertain small benefits in AD control (9% higher chance of 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: While the systematic review and meta-analysis did not show 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[16]. 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[16, 173]. This effect may be magnified in very young infants where such practices are currently commonly employed. 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 (e.g. 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 (e.g. in individual patients, 3 cycles of 2-week cross-over trials alternating between elimination vs inclusion) with jointly prespecified measures (e.g. EASI and POEM) and endpoints may be a more objective way to document response with close follow up and preventing prolonged elimination of foods[174, 175]. The **Appendix** 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[176-178]. Although elevated food allergen-specific IgE levels are commonly 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[179]. Allergen-specific IgE may also allow for greater antigen presentation by dendritic cells, which in turn facilitates increased T cell activation[180]. Further research is needed to clarify the connection, if any, of food-specific innate and adaptive immunity 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 (e.g. allergic rhinitis, asthma with relevant sensitization) may lead to benefits for multiple diseases and therefore favor AIT.
2. Values and preferences regarding SCIT versus SLIT (e.g. 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 allergen immunotherapy to horse. In contrast, a patient with dust

mite sensitization and dust mite exposure might benefit from allergen immunotherapy to dust mite.

Benefits and harms: The linked systemic review of 23 RCTs (10 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)[17]. The majority of the studies desensitized patients to house dust mites (HDM; *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae*), whereas 4 included other inhaled allergens (e.g. pollens). Patients were mostly on standard topical therapy including topical corticosteroids and moisturizers with AIT added on. The majority of the studies included poly-sensitized subjects in addition to HDM sensitization. Based on a combination of clinician-reported AD severity (e.g. SCORAD), AIT likely improved AD severity by 50% or more from baseline compared to 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 showed improvement in health-related quality of life, based on a 4-point or more improvement in dermatology life quality index (DLQI): AIT as compared to no AIT (56% vs 39%).

The main adverse effects were similar to AIT for allergic rhinitis and asthma i.e. 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 about 10% of those receiving SCIT and were rare with SLIT (0.14% systemic reaction; 1.2% discontinue).

Values and preferences: The linked systematic review[18] along with direct patient and caregiver input showed that patients with AD value non-pharmacologic therapies, safe interventions, stepping-up therapy based on severity, and a strong patient-provider relationship. They also value odorless and non-visible 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 above).

Contextual factors: Accessibility to specialists with expertise in allergen immunotherapy is required to initiate the treatment, and in order to receive SCIT, a clinician and facility capable of treating systemic allergic reactions including anaphylaxis is 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 US may be most familiar with SLIT tablets. SLIT tablets are FDA approved for dust mites, grass, ragweed for allergic rhinitis; dust mite for 12 years to 65 years; grass and ragweed 5 years to 65 years. Separate allergen immunotherapy practice parameters state there is no specific upper or lower age limit for initiating allergen immunotherapy if indications are present and after considering the absence of significant comorbid conditions and the patients' ability to complete allergen immunotherapy[181]. The **Appendix** 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 (e.g. 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, the majority of individuals with mild AD and no other allergic comorbidities will likely not pursue this treatment.
2. Values and preferences regarding SCIT versus SLIT (e.g. convenience, age, travel plans).

Benefits and harms: While 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[182, 183] beyond contributing to epidermal barrier disruption via their allergen-intrinsic enzymatic activity[184-186] and direct innate cell activation[187, 188]. These mechanisms could lead to the elaboration of multiple cytokines including IL-4, IL-13 from T cells and local production of TSLP, IL-25, IL-33, GM-CSF[55, 189, 190] by multiple cellular sources that promote skin inflammation and itch. Conversely, AIT's multiple anti-inflammatory, immunomodulatory, and pro-tolerogenic mechanisms, including induction of IL-10 production by innate cells, epithelial repair, and modulation of the JAK-STAT pathway[191-194], 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 (e.g. 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 ultraviolet 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 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 network meta-analysis showed that compared to continued standard topical treatment alone, adding dupilumab led to large improvements in multiple patient-important outcomes (**Figure 5** presents an abbreviated summary of findings from systemics network meta-analysis) 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 (4% [95%CrI 2-6%] with dupilumab versus 2% with placebo). Safety data included studies lasting 52 weeks in duration, and even longer-term (multi-year) safety data have been reported to further support this recommendation [195, 196]. Dupilumab is approved for several conditions that are often comorbid with atopic dermatitis. Benefits could therefore also include treatment of associated conditions such as prurigo nodularis, eosinophilic esophagitis, asthma, and chronic sinusitis with nasal polyps[197, 198]

Values and preferences: The linked systematic review[18] along with direct patient and caregiver input showed 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 non-visible 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, feasible, 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 but if they are administered by a health care professional (e.g. at a physician's office or at an injection clinic) 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, allergen immunotherapy 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. The optimal definition or period before designating a patient's AD as refractory to mid-high potency topical treatment is unclear. The available RCTs systematically reviewed (submitted topicals and systemics NMAs) and AD experts typically expect response to mid- or high potency topical therapy within 2-4 weeks.

Conjunctivitis can be an adverse effect of dupilumab (submitted systemics NMA). Patients may experience dry, red, itchy eyes, tearing and foreign body sensation, and may also have 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[199]. Some protocols suggest a baseline eye exam by an ophthalmologist and the use of lubricant eye drops (artificial tears) twice daily when dupilumab is initiated. Mild conjunctivitis may respond to warm compresses, lubricant eye drops and if 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 topical corticosteroid 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.[200] Some patient partners shared they preferred the medication to come to room temperature before injection, while others did not mind using soon after removal from the refrigerator. Likewise, some remarked that they found the autoinjector less painful compared to the prefilled syringe. The **Appendix** provides additional practical information and implementation considerations, including navigating vaccines/immunizations, in 1-2 page handouts.

Abbreviated summary of findings for systemic agents for AD from Systemics treatment network meta-analysis

	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%CI)**	**RD (95%CI)**	**RD (95%CI)**
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 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 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 Grading of Recommendations Assessment, Development and Evaluation 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 (submitted). MD = mean difference. RD = risk difference. CI = confidence interval. CrI = credible interval. *Although dupilumab, lebrikizumab, and tralokinumab did not demonstrate an increase in the frequency of any adverse event, they increased the frequency of conjunctivitis compared to standard care (Supplementary E4). †Abrocitinib, baricitinib, and upadacitinib also increased the frequency of viral skin infections specifically, such as herpres 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

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).

Remark: The panel has issued a strong recommendation for dupilumab or tralokinumab and a conditional recommendation for allergen immunotherapy. Individuals can be on both immunotherapy and a biologic treatment simultaneously. While the panel has not rendered an official recommendation regarding a biologic versus immunotherapy, if patients pursue only one or the other treatment, many patients might prefer dupilumab or tralokinumab over allergen immunotherapy 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), (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 network meta-analysis showed that compared to continued standard care alone, adding tralokinumab led to improvements in multiple patient-important outcomes (**Figure 5** presents an abbreviated summary of findings from Chu et al Systemics 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. Compared to 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[18] along with direct patient and caregiver input showed 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 non-visible 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 (e.g. 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 inconvenience and added coordination needs with receiving or self-injecting the medication.

Implementation considerations: While the panel strongly recommends 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 to agents targeting solely IL-13 such as tralokinumab or lebrikizumab. See the practical issues (**Appendix**) and **Recommendation 16** addressing dupilumab regarding implicit aspects of the recommendation, conjunctivitis, and injections.

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 above, 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 greater], baricitinib 2-4 mg [age 18 years or greater], upadacitinib 15-30 mg [age 12 years or greater]) over not using one of these JAK inhibitors (conditional recommendation, low quality evidence).

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 (e.g. 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 age 18 years or greater. Abrocitinib, however, is approved in ages 12 years or greater 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 age for 12 years or greater.
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:
    a) As a brief duration bridge to one of the systemic therapies
    b) Rare and intermittent use for a severe flare (e.g. erythroderma) or for social circumstances (e.g. days before a major life event).

Benefits and harms: The linked systematic review and network meta-analysis showed 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 network meta-analysis, across outcomes generally followed, according to daily dose: upadacitinib 30mg > upadacitinib 15 mg and abrocitinib 200 mg > abrocitinib 100 mg and baricitinib 2-4 mg > baricitinib 1 mg.

While mild and common harms (e.g. acne, urinary tract infection, upper respiratory 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, while serious infections such as herpetic infections (e.g. 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 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, as well as class-wide theoretical safety concerns and boxed warnings for JAK-inhibitors from the US Food and Drug Administration. Published in 2022, the Oral Rheumatoid Arthritis Trial (ORAL) Surveillance study was a 40-month, randomized, post-authorization non-inferiority trial comparing tofacitinib—an oral pan-JAK inhibitor—to tumor necrosis factor (TNF) inhibitor (adalimumab or etanercept) in patients with rheumatoid arthritis enriched for cardiovascular risk (age 50 years or older with an additional cardiovascular risk factor)[201]. 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%), 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[202], while the early available non-randomized data in AD is so far reassuring[203]. Hence, while 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 (JAK1), baricitinib (JAK1=JAK2) and upadacitinib (JAK1) are more selective than tofacitinib (JAK1=JAK2=JAK3 > TYK2). In addition, previous epidemiology studies found that patients with rheumatoid arthritis have substantially higher cardiovascular risk compared to those with AD. Finally, the ORAL trial compared tofacitinib with TNF-inhibitors, which were previously shown to reduce cardiovascular risk in rheumatologic and gastrointestinal disease. Thus, while 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 JAKibs, with and without risk factors for these outcomes, to definitively rule out a similar risk applying to them. While 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[18] and direct patient partner input showed that patients highly value medications that are both effective and safe, including preferring to avoid adverse effects such as cancer, arterial and venous thrombosis (e.g. myocardial infarction, pulmonary embolism, deep vein thrombosis), and serious infections.

The RCT findings addressing benefits and harms (submitted systemics NMA) 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 (e.g., the included 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 (e.g., 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, 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 (described below). 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[204]. Further, extensive counselling, pre-initiation bloodwork, infectious disease treatment and vaccination, and routine blood monitoring while on treatment may lead to prohibitive time required to treat[160], and limit acceptability, accessibility, feasibility and equity. Additional patient self-monitoring and the potential for modification of activities or due to comorbidities (e.g. that risk thrombosis or infection) may also affect acceptability and feasibility (e.g. time, cost).

Summary of rationale: The panel inferred that a majority of 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 (e.g. days before a major life event such as a wedding) or a brief bridge to safer systemic therapies (e.g. dupilumab or tralokinumab).

Implementation considerations: (Alphabetical) Abrocitinib, baricitinib, and upadacitinib are all immunosuppressants and therefore screening for conditions before use (e.g. 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 above. There are thus multiple implementation considerations, detailed in the **Appendix**, including drug-drug interactions, laboratory and clinical monitoring, FDA approved doses, and practical considerations. Clinicians should consider risk factors for each outcome (**Table 6**).

Cancer[205, 206]	**VTE[207]**	**ATE[208]**	**Serious infection**
UV light from excessive sun exposure, UV-based treatments, or tanning	Recent major surgery (including hip or knee arthroplasty within six weeks) [or injury]	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	Age	

Ethanol use	estrogen-containing oral contraceptives or other estrogen preparations	Hypertension	
Exposure to less common specific known carcinogens	Obesity	Dyslipidemia	
Cancer-associated inherited syndrome	Thrombophilia (hereditary or acquired [e.g. antiphospholipid syndrome]	History of hypertensive disorder of pregnancy (e.g. pre-eclampsia)	
(radon, air pollution, asbestos)	Immobility	Obesity	
Obesity	Female sex	Family history	
	Prolonged travel (air, land) >4 hours	Ethnicity	
		Male gender	
		Sedentary	
		Diet	
		Chronic kidney disease	

Table 6. Some common risk factors for cancer, venous thromboembolism (VTE), arterial thrombosis (ATE; e.g. myocardial infarction or stroke), and serious infections.

Recommendation 19: In adults and adolescents with moderate-severe AD refractory, intolerant, or unable to use mid-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 network meta-analysis showed 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 to 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; **Figure 5**). Detailed above 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 to 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 2-4 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 (e.g. 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-high potency topical treatment and systemic treatment inclusive of a biologic recommended above, the panel suggests against using azathioprine (conditional recommendation, low quality evidence).

Conditions to consider:

1. Patients that prefer a different adverse effect profile and its required monitoring, and for whom can wait a longer period of time for symptom relief may prefer azathioprine over other immunosuppressive agents. For example, while 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 to 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 to other treatments that do not address such comorbidities.

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

Values and preferences: The linked systematic review[18] showed 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: Pre-treatment blood screening (e.g. thiopurine methyltransferase TPMT testing) to minimize the risk of azathioprine harms (e.g. neutropenia) and subsequent routine laboratory monitoring is 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 to the modest benefits in two out 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 **Appendix** provides additional practical information and implementation considerations in 1-2 page handouts.

Cyclosporine

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

Conditions to consider:

1. Cyclosporine has conventionally been dosed at either low (2-3 mg/kg) or high dose (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 to 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 (e.g. 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:
    a) As a brief duration bridge to one of the systemic therapies
    b) Rare and intermittent use for a severe flare (e.g. erythroderma) or for social circumstances (e.g. days before a major life event).

Benefits and harms: The linked systematic review and network meta-analysis showed that cyclosporine may improve patient-important AD outcomes in a dose-dependent fashion (**Figure 5**, for example: 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 though indirect evidence from a network meta-analysis of RCTs in patients with psoriasis showed an increase in adverse events[209]. 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 showed dose-dependent increase in cancer risk, starting at 2 years, and increasing over 7 years[210]. 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[18] and direct patient input showed 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 patient would place a higher value on the uncertain patient-important benefits compared to 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 though patients are often transitioned to other maintenance therapies within 1-2 years. Multiple ideal body weight calculators are available for dosing. The **Appendix** provides additional practical information and implementation considerations, including examples of blood pressure, renal function and other monitoring, in 1-2 page handouts. While there may be differences between modified (microemulsion generic drug, for example, 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[211]. The two formulations are converted between each other at 1:1 dosing. Similar data are seen in comparisons of formulations in treating patients with psoriasis[212] and rheumatoid arthritis[213, 214]. Indirect evidence from randomized trials in organ transplant[215-219], non-randomized 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[220-225].

Methotrexate

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

Conditions to consider:

1. Patients that prefer a different adverse effect profile and its required monitoring, and for whom 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 avoid adverse effects (eg. stomatitis, abdominal pain) may place a greater value on avoiding these potential harms compared to 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 to other treatments that do not address such comorbidities.

Benefits and harms: The systematic review and network meta-analysis showed modest benefits with add-on methotrexate compared to continued standard care in 2 patient-important AD outcomes (**Figure 5**; AD severity RD 6 per 100; quality of life 10 per 100) and other outcomes were very uncertainty due to extremely serious imprecision.

While serious adverse events were uncommon, existing RCTs in cardiovascular disease, psoriasis, psoriatic arthritis and IBD show probably no important increase in mortality over 1-2 years. The Cardiovascular Inflammation Reduction Trial (CIRT) 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 to 82% of patients taking placebo (HR 1.17 [95%CI 1.10–1.25]). Methotrexate increased risks for skin cancer (2%), GI (RD 3%), infection (RD 4%), and pulmonary (RD 3%), and hematologic adverse events (RD 18%)[226]. In a meta-analysis of 68 trials (6938 patients), the authors also concluded an increased risk of one or more adverse events (RR 1.13 [95%CI 1.04–1.22])[227]. 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 moderate due to serious indirectness.

Values and preferences: Based on the linked systematic review of patient values and preferences[18] 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, like most other immunosuppressants, requires screening at baseline and routine blood monitoring. On average, methotrexate may cost less compared to 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 to 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 **Appendix** 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-high potency topical treatment and systemic treatment inclusive of a biologic recommended above, the panel suggests against using mycophenolate (conditional recommendation, low certainty evidence).

Conditions to consider:

1. Patients that prefer a different adverse effect profile and its required monitoring, and for whom 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 cyclosporine (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 to 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 to other treatments that do not address such comorbidities.

Benefits and harms: The systematic review and network meta-analysis showed 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 (**Figure 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) is, however, sparse and therefore of also low certainty when applied to AD.

Values and preferences: Based on the linked systematic review of patient values and preferences[18] 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, like 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 to the uncertain modest benefits, especially when considering safer or more certain alternatives. The low certainty evidence drove the conditional recommendation.

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

Narrow-band ultraviolet B light (NB-UVB)

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

Conditions to consider:

1. Patients that 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 that are pregnant or planning to become pregnant may prefer NB-UVB.
2. NB-UVB can be difficult to access and hence, patients that must travel large distances, incur costs (e.g. parking, gas, time), or face long wait times may prefer other treatments over NB-UVB.
3. Patients with photo-responsive comorbidities, such as psoriasis or vitiligo, may prefer to use NB-UVB to address more than one condition, compared to 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:
    a) 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 ultraviolet light A band (UVA) alone or with psoralen (PUVA), as UVA-based therapies are associated with more harms and have even lower certainty for benefits in AD (submitted systemics treatment NMA and Cochrane review[228]).

While the panel suggested oral JAK inhibitors, cyclosporine or NB-UVB in this population, they did not yet issue a formal recommendation addressing one over the other. Patients, however, will likely pursue only one out 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 (e.g. patients refractory to any one of the three interventions).

Benefits and harms: The linked systematic review and network meta-analysis showed that clinic-based NB-UVB 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 (**Figure 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 >200 sessions (HR 2.27 [95%CI 1.53–3.37]). A common adverse event is erythema. Clinical experts remarked that long term UVB exposure might induce darkening of the skin and that this might be desired or not based on patient preference.

Certainty of evidence for AD severity and sleep disturbance was low due to very serious imprecision (small sample sizes and wide confidence intervals), 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 and direct patient input showed 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-UVB, 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 non-adherence (adjusted odds ratio, 2.06 [95%CI 1.30-3.26])[229]. Centers with NB-UVB 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 **Appendix** provides expanded discussion about practical considerations. The National Eczema Association provides a patient handout addressing phototherapy: https://nationaleczema.org/eczema/treatment/phototherapy/ . While NB-UVB is also available using home devices, they lack robust evidence addressing their efficacy and safety, and comparability to clinic-based NB-UVB, 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 network meta-analysis showed that systemic corticosteroids improved AD severity but had little to no improvement in quality of life, itch, or sleep disturbance (**Figure 5**). Hence, the benefits were low certainty due to very

serious imprecision. The trials often reported that benefits were transient and disease activity rebounded upon 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 impairments[230, 231]. 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), fracture (1.87 [1.69-2.07]; 27 vs 14 per 1000)[230]. 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) of systemic corticosteroids and long-term systemic corticosteroid use cause a range of common and serious harms[230-234]. Adverse effects of repeated use include fragility fractures secondary to osteoporosis, heart attack/stroke, diabetes, and obesity.

Values and preferences: The linked systematic review and direct patient input showed that patients value rapid-acting interventions that are both safe and effective. While 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 emergency room, urgent care centers or urgent clinician visits, consumes 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 versus their uncertain important benefits. The significant harms and burdens in relation to their often transient benefit and low certainty evidence drove the conditional recommendation. The **Appendix** provides additional practical information and implementation considerations in 1-2 page handouts.

<u>Mechanisms of action of systemic treatments</u>

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 interleukin-4 (IL-4) receptor alpha subunit. By specifically targeting IL4Rα, it inhibits IL-4 and interleukin-13 (IL-13) signaling to reduce cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and immunoglobulin E. IL-4 and IL-13 drive the type 2 inflammation in AD.[235-237]

Tralokinumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody that specifically binds to interleukin-13 (IL-13) inhibiting its ability to bind receptors[238]. IL-13 is a pleiotropic T-helper type 2 (TH2) cytokine that contributes to skin barrier disruption, inflammation, increased risk of skin infections, itch signaling, and epidermal hyperplasia.

Janus kinases (JAK) are key components of the JAK/STAT pathway for cytokine receptor signaling which is an integral part of the inflammatory pathophysiology of AD[239]. JAK1 has an important role in signaling via 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[240]. 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. Increases selectivity of the second-generation agents may reduce associated adverse events[241].

Azathioprine is a purine synthesis inhibitor that reduces leukocyte proliferation. Azathioprine interferes with T-cell, B-cell, and antigen-presenting cell functions[242].

Cyclosporine is an immunomodulatory medication that inhibits interleukin-2 (IL-2) signaling and the function of T lymphocytes via a complex formed between cyclosporine and cyclophilin[243]. Suppression of IL-2 inhibits calcineurin and signal transduction mediated by T-cell receptor activation and in AD, downregulation of levels of TH2-, TH22-, and some TH17-related molecules (ie, IL-13, IL-22, CCL17, S100As, and elafin/peptidase inhibitor 3), and modulation of epidermal hyperplasia and differentiation measures[244].

Methotrexate is an anti-metabolite that interferes with folic acid metabolism which signals an anti-inflammatory response.

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[245-247]

NB-UVB reverses epidermal defects and alters cutaneous inflammatory mileu[248, 249].

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[250] or Indigenous Ways of Knowing[108]. If these interventions or others become more commonly used, we hope to address them in subsequent living guidelines in which individual recommendations are updated or added as new evidence arise. Future research may provide robust evidence regarding these interventions.

AD, like 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 (e.g. NIH/NIAID), and private organizations - to promote comparative effectiveness and safety of approved medications and their optimal use in treatment pathways. Robust data addressing patients that 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 **Appendix** 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 are compared against each other). These have significant limitations including being unable to adequately assess adverse events, equally important to efficacy assessments, and ignores the systemic inflammation[251, 252] 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, e.g. topical corticosteroids, calcineurin inhibitors 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 (e.g. 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 sub-analyses must clearly report the parent main trial registration number (e.g., NCT) and main publication citation, specifying which data, if any, are unique to the sub-analyses 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 re-randomized to group B from week 16 to 52, investigators should separately report baseline and outcome data for participants from week 0-16 assigned to Group A, then separately for the same participants assigned to group B from week 16-52 and should clearly report characteristics of participants in both periods. Should there be participants that receive the same intervention in both periods (e.g. from the example above, the same intervention from weeks 0 to 52), investigators should clearly report the outcome data for this subgroup of participants. Re-randomized participants' outcome data should be reported in isolation, before separate analyses that pool them with those participants that did not undergo re-randomization.
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 (e.g. 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 (e.g. 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 (e.g. baseline EASI, SCORAD, POEM, itch, sleep disturbance, QoL, etc.).
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 (e.g. clinicaltrials.gov). Enforcement must be at multiple levels. For example, in March 2023, the UK 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 cross-over (what is commonly 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 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 employed for time-to-response to therapy at minimally important differences (e.g. 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. Re-prioritization of outcomes is needed. Less outcomes per study should be collected and more focus should be placed on assessing patient-important ones. e.g. 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, i.e. robust multiyear comparative studies. The framework addressing the safety of TCIs presented in the **Guideline main text**, along with the **Appendix** provides additional study design considerations.
19. 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. Due to the relapsing nature of AD, studies should separate adverse reactions from worsening of pre-existing AD (or its known complications such as localized infections) as this obfuscates assessment of treatment-specific harms (e.g. placebo experiences more adverse events due to worsening AD, while the intervention may improve in AD and therefore the study end up reporting that the treatment group, compared to the placebo group, had less overall adverse events). This further reinforces the need for active comparator trials.

Actively promote equity, diversity, and inclusiveness in clinical trials and research addressing AD

20. All patients with AD deserve to access novel medicines and randomized trials, yet racial and ethnic under-representation is common in current AD trials[253, 254] and historically racialized groups are often suboptimally reported[255]. Active engagement and outreach to equitably include diverse populations is needed in future AD RCTs and research. Reporting of race and ethnicity should follow updated standards[81, 256].
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 AD

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 adverse events[257]. 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 AAAAI/ACAAI JTFPP Atopic Dermatitis guidelines and what are others saying?

This JTFPP guideline represents an evolution in trustworthy allergy guidelines[1] and is 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 guideline 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 guideline focused 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, 114]; 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 European Dermatology Foundation has recently published a guideline on systemic therapy in AD and maintains a website for Living EuroGuiDerm guideline for the systemic treatment of atopic eczema. 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 recommend cyclosporine and the two 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 intervenitons, thereby encouraging shared decision-making. Similarly, the EuroGuiDerm guideline provides weak (conditional) recommendations in favor for azathioprine, methotrexate and systemic glucorticosteroids, while 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. This may include, for example, formal assessment of lebrikizumab, nemolizumab, tapinarof, 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 epidemiology, pathophysiology, clinical evidence, and patient testimonials[258] show 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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References

1. Agarwal A, Chen L, Capozza K, Roberts A, Golden DBK, Shaker MS, et al. Trustworthy Patient-Centered Guidelines: Insights From Atopic Dermatitis and a Proposal for the Future. *J Allergy Clin Immunol Pract.* 2022;10:2875-2877.
2. Capozza K, Vastrup A, Proctor A, Roberts A, Picozza M, Manion R, et al. The sound of silence: where are the voices of patients in eczema guideline development? *Br J Dermatol.* 2022;187:1005-1006.
3. Arents BWM, van Zuuren EJ, Vermeulen S, Schoones JW, Fedorowicz Z. Global Guidelines in Dermatology Mapping Project (GUIDEMAP), a systematic review of atopic dermatitis clinical practice guidelines: are they clear, unbiased, trustworthy and evidence based (CUTE)? *Br J Dermatol.* 2022;186:792-802.
4. Schünemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso-Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE – A statement by the GRADE guidance group. *Journal of Clinical Epidemiology.* 2023;159:79-84.
5. Wheeler KE, Chu DK, Schneider L. What Parents Should Know About Atopic Dermatitis. *JAMA Pediatr.* 2022;176:1156.
6. Whalen-Browne A, Williams HC, Chu DK. Managing atopic dermatitis in infants. *Canadian Medical Association Journal.* 2022;194:E1485.
7. Chu DK, Golden DBK, Guyatt GH. Translating Evidence to Optimize Patient Care Using GRADE. *J Allergy Clin Immunol Pract.* 2021;9:4221-4230.
8. Evidence-Based Medicine Working G. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA.* 1992;268:2420-2425.
9. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol.* 2013;131:295-299 e291-227.
10. Lio PA, Lee M, LeBovidge J, Timmons KG, Schneider L. Clinical Management of Atopic Dermatitis: Practical Highlights and Updates from the Atopic Dermatitis Practice Parameter 2012. *Journal of Allergy and Clinical Immunology-in Practice.* 2014;2:361-369.
11. Boguniewicz M. Atopic dermatitis: The updated practice parameter and beyond. *Allergy and Asthma Proceedings.* 2014;35:429-434.
12. Leung DYM, Nicklas RA, Li JT, Bernstein IL, Blessing-Moore J, Boguniewicz M, et al. Disease management of atopic dermatitis: an updated practice parameter. *ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY.* 2004;93:S1-S21.
13. Leung DYM, Hanifin JM, Charlesworth EN, Li JT, Bernstein IL, Berger WE, et al. Disease management of atopic dermatitis: a practice parameter. *ANNALS OF ALLERGY ASTHMA & IMMUNOLOGY.* 1997;79:197-211.
14. Devasenapathy N, Chu A, Wong M, Srivastava A, Ceccacci R, Lin C, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. *The Lancet Child & Adolescent Health.* 2023;7:13-25.
15. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. *Ann Allergy Asthma Immunol.* 2022;128:660-668.e669.
16. Oykhman P, Dookie J, Al-Rammahy H, De Benedetto A, Asiniwasis RN, LeBovidge J, et al. Dietary elimination for the treatment of atopic dermatitis: a systematic review and meta-analysis. *The Journal of Allergy and Clinical Immunology: In Practice.* 2022;10:2657-2666 e2658.
17. Yepes-Nuñez JJ, Guyatt GH, Gómez-Escobar LG, Pérez-Herrera LC, Chu AWL, Ceccaci R, et al. Allergen immunotherapy for atopic dermatitis: Systematic review and meta-analysis of benefits and harms. *J Allergy Clin Immunol.* 2023;151:147-158.

18. Maleki-Yazdi KA, Heen AF, Zhao IX, Guyatt GH, Suzumura EA, Makhdami N, et al. Values and Preferences of Patients and Caregivers Regarding Treatment of Atopic Dermatitis (Eczema): A Systematic Review. *JAMA Dermatol.* 2023.

19. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM, et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017*. *British Journal of Dermatology.* 2021;184:304-309.

20. Silverberg JI, Barbarot S, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. Atopic dermatitis in the pediatric population: A cross-sectional, international epidemiologic study. *Ann Allergy Asthma Immunol.* 2021;126:417-428.e412.

21. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *Journal of Allergy and Clinical Immunology.* 2009;124:1251-1258.e1223.

22. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. *J Allergy Clin Immunol.* 2013;132:1132-1138.

23. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol.* 2018;121:340-347.

24. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. *J Am Acad Dermatol.* 2019;80:1526-1532.e1527.

25. Vakharia PP, Chopra R, Silverberg JI. Systematic Review of Diagnostic Criteria Used in Atopic Dermatitis Randomized Controlled Trials. *Am J Clin Dermatol.* 2018;19:15-22.

26. Brenninkmeijer EE, Schram ME, Leeflang MM, Bos JD, Spuls PI. Diagnostic criteria for atopic dermatitis: a systematic review. *Br J Dermatol.* 2008;158:754-765.

27. Dizon MP, Yu AM, Singh RK, Wan J, Chren MM, Flohr C, et al. Systematic review of atopic dermatitis disease definition in studies using routinely collected health data. *Br J Dermatol.* 2018;178:1280-1287.

28. Hanifin JR, G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol.* 1980;92:44-47.

29. Williams HC, Burney PG, Hay RJ, Archer CB, Shipley MJ, Hunter JJ, et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol.* 1994;131:383-396.

30. Simpson EL, Keck LE, Chalmers JR, Williams HC. How should an incident case of atopic dermatitis be defined? A systematic review of primary prevention studies. *J Allergy Clin Immunol.* 2012;130:137-144.

31. Larsen FS, Hanifin JM. Epidemiology of atopic dermatitis. *Immunology and Allergy Clinics of North America.* 2002;22:1-24.

32. Bosma AL, Ascott A, Iskandar R, Farquhar K, Matthewman J, Langendam MW, et al. Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics. *J Eur Acad Dermatol Venereol.* 2022;36:807-819.

33. Birdi G, Cooke R, Knibb RC. Impact of atopic dermatitis on quality of life in adults: a systematic review and meta-analysis. *Int J Dermatol.* 2020;59:e75-e91.

34. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol.* 2006;155:145-151.

35. Williams HC, Schmitt J, Thomas KS, Spuls PI, Simpson EL, Apfelbacher CJ, et al. The HOME Core outcome set for clinical trials of atopic dermatitis. *J Allergy Clin Immunol.* 2022;149:1899-1911.

36. Schmitt J, Spuls PI, Thomas KS, Simpson E, Furue M, Deckert S, et al. The Harmonising Outcome Measures for Eczema (HOME) statement to assess clinical signs of atopic eczema in trials. *J Allergy Clin Immunol.* 2014;134:800-807.

37. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol.* 2016;74:491-498.

38. Cheng BT, Paller AS, Griffith JW, Silverberg JI, Fishbein AB. Burden and characteristics of skin pain among children with atopic dermatitis. *J Allergy Clin Immunol Pract.* 2022;10:1104-1106.e1101.

39. Vakharia PP, Chopra R, Sacotte R, Patel KR, Singam V, Patel N, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol.* 2017;119:548-552.e543.

40. Chang YS, Chiang BL. Sleep disorders and atopic dermatitis: A 2-way street? *J Allergy Clin Immunol.* 2018;142:1033-1040.

41. Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA, et al. Association of Atopic Dermatitis With Sleep Quality in Children. *JAMA Pediatr.* 2019;173:e190025.

42. Fishbein AB, Vitaterna O, Haugh IM, Bavishi AA, Zee PC, Turek FW, et al. Nocturnal eczema: Review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. *Journal of Allergy and Clinical Immunology.* 2015;136:1170-1177.

43. Ghio D, Greenwell K, Muller I, Roberts A, McNiven A, Santer M. Psychosocial needs of adolescents and young adults with eczema: A secondary analysis of qualitative data to inform a behaviour change intervention. *Br J Health Psychol.* 2021;26:214-231.

44. Capozza K, Schwartz A, Lang JE, Chalmers J, Camilo J, Abuabara K, et al. Impact of childhood atopic dermatitis on life decisions for caregivers and families. *J Eur Acad Dermatol Venereol.* 2022;36:e451-e454.

45. Capozza K, Gadd H, Kelley K, Russell S, Shi V, Schwartz A. Insights From Caregivers on the Impact of Pediatric Atopic Dermatitis on Families: "I'm Tired, Overwhelmed, and Feel Like I'm Failing as a Mother". *Dermatitis.* 2020;31:223-227.

46. Ramirez FD, Chen S, Langan SM, Prather AA, McCulloch CE, Kidd SA, et al. Assessment of Sleep Disturbances and Exhaustion in Mothers of Children With Atopic Dermatitis. *JAMA Dermatol.* 2019;155:556-563.

47. Barbarot S, Silverberg JI, Gadkari A, Simpson EL, Weidinger S, Mina-Osorio P, et al. The Family Impact of Atopic Dermatitis in the Pediatric Population: Results from an International Cross-sectional Study. *J Pediatr.* 2022;246:220-226.e225.

48. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet.* 2020;396:345-360.

49. Weidinger S, Novak N. Atopic dermatitis. *Lancet.* 2016;387:1109-1122.

50. Schuler CFIV, Billi AC, Maverakis E, Tsoi LC, Gudjonsson JE. Novel insights into atopic dermatitis. *Journal of Allergy and Clinical Immunology.*

51. Ong PY. Atopic dermatitis: Is innate or adaptive immunity in control? A clinical perspective. *Front Immunol.* 2022;13:943640.

52. Bakker D, de Bruin-Weller M, Drylewicz J, van Wijk F, Thijs J. Biomarkers in atopic dermatitis. *Journal of Allergy and Clinical Immunology.* 2023;151:1163-1168.

53. Yoshida T, Beck LA, De Benedetto A. Skin barrier defects in atopic dermatitis: From old idea to new opportunity. *Allergol Int.* 2022;71:3-13.

54. Martin MJ, Estravís M, García-Sánchez A, Dávila I, Isidoro-García M, Sanz C. Genetics and Epigenetics of Atopic Dermatitis: An Updated Systematic Review. *Genes (Basel).* 2020;11.

55. Chu DK, Llop-Guevara A, Walker TD, Flader K, Goncharova S, Boudreau JE, et al. IL-33, but not thymic stromal lymphopoietin or IL-25, is central to mite and peanut allergic sensitization. *J Allergy Clin Immunol.* 2013;131:187-200 e181-188.

56. Wang V, Boguniewicz J, Boguniewicz M, Ong PY. The infectious complications of atopic dermatitis. *Ann Allergy Asthma Immunol.* 2021;126:3-12.

57. Ong PY, Boguniewicz J, Chu DK. Skin antiseptics for atopic dermatitis: dissecting facts from fiction. *The Journal of Allergy and Clinical Immunology In Practice.* 2023.

58. Garg NK, Silverberg JI. Eczema is associated with osteoporosis and fractures in adults: a US population-based study. *J Allergy Clin Immunol.* 2015;135:1085-1087.e1082.
59. Silverberg JI. Comorbidities and the impact of atopic dermatitis. *Ann Allergy Asthma Immunol.* 2019;123:144-151.
60. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *J Invest Dermatol.* 2017;137:18-25.
61. Paller A, Jaworski JC, Simpson EL, Boguniewicz M, Russell JJ, Block JK, et al. Major Comorbidities of Atopic Dermatitis: Beyond Allergic Disorders. *Am J Clin Dermatol.* 2018;19:821-838.
62. Thyssen JP, Halling AS, Schmid-Grendelmeier P, Guttman-Yassky E, Silverberg JI. Comorbidities of atopic dermatitis-what does the evidence say? *J Allergy Clin Immunol.* 2023.
63. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann Allergy Asthma Immunol.* 2018;121:604-612.e603.
64. Hou A, Silverberg JI. Predictors and age-dependent pattern of psychologic problems in childhood atopic dermatitis. *Pediatr Dermatol.* 2021;38:606-612.
65. Jackson-Cowan L, Silverberg JI. Longitudinal course of cognitive impairment in patients with atopic dermatitis. *Arch Dermatol Res.* 2023.
66. Beck KM, Seitzman GD, Yang EJ, Sanchez IM, Liao W. Ocular Co-Morbidities of Atopic Dermatitis. Part I: Associated Ocular Diseases. *Am J Clin Dermatol.* 2019;20:797-805.
67. Beck KM, Seitzman GD, Yang EJ, Sanchez IM, Liao W. Ocular Co-Morbidities of Atopic Dermatitis. Part II: Ocular Disease Secondary to Treatments. *American Journal of Clinical Dermatology.* 2019;20:807-815.
68. Ravn NH, Ahmadzay ZF, Christensen TA, Larsen HHP, Loft N, Raevdal P, et al. Bidirectional association between atopic dermatitis, conjunctivitis, and other ocular surface diseases: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology.* 2021;85:453-461.
69. Matthewman J, Mansfield KE, Prieto-Alhambra D, Mulick AR, Smeeth L, Lowe KE, et al. Atopic Eczema-Associated Fracture Risk and Oral Corticosteroids: A Population-Based Cohort Study. *J Allergy Clin Immunol Pract.* 2022;10:257-266.e258.
70. Lowe KE, Mansfield KE, Delmestri A, Smeeth L, Roberts A, Abuabara K, et al. Atopic eczema and fracture risk in adults: A population-based cohort study. *J Allergy Clin Immunol.* 2020;145:563-571.e568.
71. Strom MA, Silverberg JI. Associations of Physical Activity and Sedentary Behavior with Atopic Disease in United States Children. *J Pediatr.* 2016;174:247-253.e243.
72. Lin TL, Wu CY, Yen JJ, Juan CK, Chang YL, Ho HJ, et al. Fracture risks in patients with atopic dermatitis: A nationwide matched cohort study. *Ann Allergy Asthma Immunol.* 2021;127:667-673.e662.
73. Pandher K, Ghamrawi RI, Heron CE, Feldman SR. Controversial cardiovascular and hematologic comorbidities in atopic dermatitis. *Archives of Dermatological Research.* 2021;314:317-324.
74. Silverberg JI. Association between adult atopic dermatitis, cardiovascular disease, and increased heart attacks in three population-based studies. *Allergy.* 2015;70:1300-1308.
75. Ascott A, Mulick A, Yu AM, Prieto-Merino D, Schmidt M, Abuabara K, et al. Atopic eczema and major cardiovascular outcomes: A systematic review and meta-analysis of population-based studies. *J Allergy Clin Immunol.* 2019;143:1821-1829.
76. Smith Begolka W, Chovatiya R, Thibau IJ, Silverberg JI. Financial Burden of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. *Dermatitis.* 2021;32:S62-s70.

77. Chovatiya R, Begolka WS, Thibau IJ, Silverberg JI. Impact and Associations of Atopic Dermatitis Out-of-Pocket Health Care Expenses in the United States. *Dermatitis.* 2022;33:S43-s51.
78. Bukstein DA, Friedman A, Gonzalez Reyes E, Hart M, Jones BL, Winders T. Impact of Social Determinants on the Burden of Asthma and Eczema: Results from a US Patient Survey. *Adv Ther.* 2022;39:1341-1358.
79. United States Census Bureau. 2020 Census Statistics Highlight Local Population Changes and Nation's Racial and Ethnic Diversity: Press Release Number CB21-CN.55*.* Vol 2023. 2021-10-08 ed: United States government; 2021.
80. Canada" S. Immigration and ethnocultural diversity statistics*.* Vol 2023: Government of Canada; 2023.
81. Lu C, Ahmed R, Lamri A, Anand SS. Use of race, ethnicity, and ancestry data in health research. *PLOS Global Public Health.* 2022;2:e0001060.
82. Davis CM, Apter AJ, Casillas A, Foggs MB, Louisias M, Morris EC, et al. Health disparities in allergic and immunologic conditions in racial and ethnic underserved populations: A Work Group Report of the AAAAI Committee on the Underserved. *J Allergy Clin Immunol.* 2021;147:1579-1593.
83. Martinez A, de la Rosa R, Mujahid M, Thakur N. Structural racism and its pathways to asthma and atopic dermatitis. *J Allergy Clin Immunol.* 2021;148:1112-1120.
84. Ogbogu PU, Capers Qt, Apter AJ. Disparities in Asthma and Allergy Care: What Can We Do? *J Allergy Clin Immunol Pract.* 2021;9:663-669.
85. Croce EA, Levy ML, Adamson AS, Matsui EC. Reframing racial and ethnic disparities in atopic dermatitis in Black and Latinx populations. *JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY.* 2021;148:1104-1111.
86. Girolomoni G, de Bruin-Weller M, Aoki V, Kabashima K, Deleuran M, Puig L, et al. Nomenclature and clinical phenotypes of atopic dermatitis. *Therapeutic Advances in Chronic Disease.* 2021;12:20406223211002979.
87. Vachiramon V, Tey HL, Thompson AE, Yosipovitch G. Atopic dermatitis in African American children: addressing unmet needs of a common disease. *Pediatr Dermatol.* 2012;29:395-402.
88. Kaufman BP, Guttman-Yassky E, Alexis AF. Atopic dermatitis in diverse racial and ethnic groups—Variations in epidemiology, genetics, clinical presentation and treatment. *Experimental Dermatology.* 2018;27:340-357.
89. Ben-Gashir MA, Seed PT, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *British Journal of Dermatology.* 2002;147:920-925.
90. Zhao CY, Wijayanti A, Doria MC, Harris AG, Jain SV, Legaspi KN, et al. The reliability and validity of outcome measures for atopic dermatitis in patients with pigmented skin: A grey area. *Int J Womens Dermatol.* 2015;1:150-154.
91. "American College of Allergy AIAatAANA. Eczema in Skin of Color*.* Vol 20232023.
92. Association" NE. Eczema & Skin of Color, Building Our Community One Story at a Time*.* Vol 2023: National Eczema Association; 2023.
93. Narla S, Heath CR, Alexis A, Silverberg JI. Racial disparities in dermatology. *Arch Dermatol Res.* 2022:1-9.
94. Chen V, Akhtar S, Zheng C, Kumaresan V, Nouri K. Assessment of Changes in Diversity in Dermatology Clinical Trials Between 2010-2015 and 2015-2020: A Systematic Review. *JAMA Dermatol.* 2022;158:288-292.
95. Pandya AG, Alexis AF, Berger TG, Wintroub BU. Increasing racial and ethnic diversity in dermatology: A call to action. *Journal of the American Academy of Dermatology.* 2016;74:584-587.
96. Nomura T, Wu J, Kabashima K, Guttman-Yassky E. Endophenotypic Variations of Atopic Dermatitis by Age, Race, and Ethnicity. *Journal of Allergy and Clinical Immunology-in Practice.* 2020;8:1840-1852.
97. Simpson EL, De Benedetto A, Boguniewicz M, Ong PY, Lussier S, Villarreal M, et al. Phenotypic and Endotypic Determinants of Atopic Dermatitis Severity From the

Atopic Dermatitis Research Network (ADRN) Registry. *The Journal of Allergy and Clinical Immunology: In Practice.* 2023.

98. Davis CM, Flohr C, Gupta MR, Koplin JJ. Managing Atopic Dermatitis in Patients With Skin of Color. *The Journal of Allergy and Clinical Immunology: In Practice.* 2023;11:1376-1383.

99. Janumpally SR, Feldman SR, Gupta AK, Fleischer AB, Jr. In the United States, Blacks and Asian/Pacific Islanders Are More Likely Than Whites to Seek Medical Care for Atopic Dermatitis. *Archives of Dermatology.* 2002;138:634-637.

100. Al-Obaydi S, Craig TJ, Al-Shaikhly T. Racial and ethnic disparities in the treatment of patients with atopic dermatitis in the United States: A retrospective matched cohort study. *The Journal of Allergy and Clinical Immunology: In Practice.*

101. Wan J, Margolis DJ, Mitra N, Hoffstad OJ, Takeshita J. Racial and Ethnic Differences in Atopic Dermatitis-Related School Absences Among US Children. *JAMA Dermatol.* 2019;155:973-975.

102. Wan J, Oganisian A, Spieker AJ, Hoffstad OJ, Mitra N, Margolis DJ, et al. Racial/Ethnic Variation in Use of Ambulatory and Emergency Care for Atopic Dermatitis among US Children. *J Invest Dermatol.* 2019;139:1906-1913.e1901.

103. Bell MA, Whang KA, Thomas J, Aguh C, Kwatra SG. Racial and Ethnic Disparities in Access to Emerging and Frontline Therapies in Common Dermatological Conditions: A Cross-Sectional Study. *J Natl Med Assoc.* 2020;112:650-653.

104. Morenz AM, Wescott S, Mostaghimi A, Sequist TD, Tobey M. Evaluation of Barriers to Telehealth Programs and Dermatological Care for American Indian Individuals in Rural Communities. *JAMA Dermatol.* 2019;155:899-905.

105. Nguyen B, Bray FN. Access to dermatologic care in Indigenous American communities. *Journal of the American Academy of Dermatology.* 2022;87:904-906.

106. Zullo SM, M; Shi, VY. The epidemiology of xerosis, eczema, and skin care habits of Native Americans. *Journal of the American Academy of Dermatology.* 2019;81:AB133.

107. Centre FNIG. National Report of the First Nations Regional Health Survey Phase 3: Volume One. Vol 1. Ottawa: First Nations Information Governance Centre; 2018:1-181.

108. Barnhardt R, Kawagley AO. Indigenous Knowledge Systems and Alaska Native Ways of Knowing. *Anthropology & Education Quarterly.* 2005;36:8-23.

109. Tsosie RLG, Anne D.; Harrington, Jennifer; Wu, Ke; Thomas, Aaron; Chase, Stephan; Barnett, D'Shane; Hill, Salena Beaumont; Belcourt, Annjeanette; Brown, Blakely; Sweetgrass-She Kills, Ruth Plenty. The Six Rs of Indigenous Research. *Tribal College Journal of American Indian Higher Education.* 2022;33.

110. Asiniwasis RN, Heck E, Amir Ali A, Ogunyemi B, Hardin J. Atopic dermatitis and skin infections are a poorly documented crisis in Canada's Indigenous pediatric population: It's time to start the conversation. *Pediatric Dermatology.* 2021;38:188-189.

111. Sabin JA. Tackling Implicit Bias in Health Care. *New England Journal of Medicine.* 2022;387:105-107.

112. Pritlove C, Juando-Prats C, Ala-leppilampi K, Parsons JA. The good, the bad, and the ugly of implicit bias. *The Lancet.* 2019;393:502-504.

113. Corbett M, Allen A, Bobo N, Foggs MB, Fonacier LS, Gupta R, et al. Proposed solutions by the American College of Allergy, Asthma, and Immunology and advocacy experts to address racial disparities in atopic dermatitis and food allergy. *Annals of Allergy, Asthma & Immunology.* 2023;130:392-396.e392.

114. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-926.

115. Dewidar O, Lotfi T, Langendam MW, Parmelli E, Saz Parkinson Z, Solo K, et al. Good or best practice statements: proposal for the operationalisation and implementation of GRADE guidance. *BMJ Evid Based Med.* 2022.

116. Schünemann HJ, Wiercioch W, Etxeandia I, Falavigna M, Santesso N, Mustafa R, et al. Guidelines 2.0: systematic development of a comprehensive checklist for a successful guideline enterprise. *Canadian Medical Association Journal.* 2014;186:E123.

117. Chen Y, Yang K, Marušić A, Qaseem A, Meerpohl JJ, Flottorp S, et al. A Reporting Tool for Practice Guidelines in Health Care: The RIGHT Statement. *Annals of Internal Medicine.* 2016;166:128-132.

118. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ.* 2010;182:E839-842.

119. Graham R MM, Miller Wolman D, et al., editors. *Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines*. Washington (DC): National Academies Press (US); 2011.

120. Schünemann HJ, Al-Ansary LA, Forland F, Kersten S, Komulainen J, Kopp IB, et al. Guidelines International Network: Principles for Disclosure of Interests and Management of Conflicts in Guidelines. *Annals of Internal Medicine.* 2015;163:548-553.

121. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *Journal of Clinical Epidemiology.* 2011;64:395-400.

122. Schmitt J, Langan S, Deckert S, Svensson A, von Kobyletzki L, Thomas K, et al. Assessment of clinical signs of atopic dermatitis: a systematic review and recommendation. *J Allergy Clin Immunol.* 2013;132:1337-1347.

123. Chu DK, Brignardello-Petersen R, Guyatt GH, Ricci C, Genuneit J. Method's corner: Allergist's guide to network meta-analysis. *Pediatr Allergy Immunol.* 2022;33:e13609.

124. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, et al. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ.* 2016;353:i2016.

125. Brignardello-Petersen R, Tomlinson G, Florez I, Rind DM, Chu D, Morgan R, et al. GRADE Concept Article 5: Addressing intransitivity in a network meta-analysis. *J Clin Epidemiol.* 2023.

126. Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. *Bmj.* 2023;381:e074495.

127. van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database of Systematic Reviews.* 2017;2017:CD012119.

128. Ridd MJ, Santer M, MacNeill SJ, Sanderson E, Wells S, Webb D, et al. Effectiveness and safety of lotion, cream, gel, and ointment emollients for childhood eczema: a pragmatic, randomised, phase 4, superiority trial. *The Lancet Child & Adolescent Health.* 2022;6:522-532.

129. Ridd MJ, Roberts A, Grindlay D, Williams HC. Which emollients are effective and acceptable for eczema in children? *Bmj-British Medical Journal.* 2019;367:l5882.

130. Chopra R, Vakharia PP, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for Eczema Area and Severity Index (EASI), modified EASI, Scoring Atopic Dermatitis (SCORAD), objective SCORAD, Atopic Dermatitis Severity Index and body surface area in adolescents and adults with atopic dermatitis. *Br J Dermatol.* 2017;177:1316-1321.

131. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol.* 2013;169:1326-1332.

132. Vakharia PP, Chopra R, Sacotte R, Patel N, Immaneni S, White T, et al. Severity strata for five patient-reported outcomes in adults with atopic dermatitis. *British Journal of Dermatology.* 2018;178:925-930.

133. Salek MS, Jung S, Brincat-Ruffini LA, MacFarlane L, Lewis-Jones MS, Basra MKA, et al. Clinical experience and psychometric properties of the Children's Dermatology Life Quality Index (CDLQI), 1995-2012. *British Journal of Dermatology.* 2013;169:734-759.
134. Finlay AY, Sampogna F. What do scores mean? Informed interpretation and clinical judgement are needed. *British Journal of Dermatology.* 2018;179:1021-1022.
135. Kunz B, Oranje AP, Labrèze L, Stalder J-F, Ring J, Taïeb A. Clinical Validation and Guidelines for the SCORAD Index: Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology.* 2009;195:10-19.
136. Hongbo Y, Thomas CL, Harrison MA, Sam Salek M, Finlay AY. Translating the Science of Quality of Life into Practice: What Do Dermatology Life Quality Index Scores Mean? *Journal of Investigative Dermatology.* 2005;125:659-664.
137. Waters A, Sandhu D, Beattie P, Ezughah F, Lewis-Jones S. *Severity stratification of Children's Dermatology Life Quality Index (CDLQI) scores*2010.
138. Li Y, Han T, Li W, Li Y, Guo X, Zheng L. Efficacy of health education on treatment of children with atopic dermatitis: a meta-analysis of randomized controlled trials. *Arch Dermatol Res.* 2020;312:685-695.
139. Waldecker A, Malpass A, King A, Ridd MJ. Written action plans for children with long-term conditions: A systematic review and synthesis of qualitative data. *Health Expect.* 2018;21:585-596.
140. Rork JF, Sheehan WJ, Gaffin JM, Timmons KG, Sidbury R, Schneider LC, et al. Parental Response to Written Eczema Action Plans in Children With Eczema. *Archives of Dermatology.* 2012;148:391-392.
141. Ntuen E, Taylor SL, Kinney M, O'Neill JL, Krowchuk DP, Feldman SR. Physicians' perceptions of an eczema action plan for atopic dermatitis. *J Dermatolog Treat.* 2010;21:28-33.
142. Thandi CS, Constantinou S, Vincent R, Ridd MJ. Where and how have written action plans for atopic eczema/dermatitis been developed and evaluated? Systematic review. *Skin Health Dis.* 2023;3:e213.
143. Utley C, Gold MH, Hall M. Development and Evaluation of an Atopic Dermatitis Care Plan for Providers. *Journal of Drugs in Dermatology.* 2020;19:950-955.
144. Brown J, Weitz NW, Liang A, Stockwell MS, Friedman S. Does an Eczema Action Plan Improve Atopic Dermatitis? A Single-Site Randomized Controlled Trial. *Clin Pediatr (Phila).* 2018;57:1624-1629.
145. Shi VY, Nanda S, Lee K, Armstrong AW, Lio PA. Improving Patient Education With an Eczema Action Plan: A Randomized Controlled Trial. *JAMA Dermatology.* 2013;149:481-483.
146. Santer M, Muller I, Becque T, Stuart B, Hooper J, Steele M, et al. Eczema Care Online behavioural interventions to support self-care for children and young people: two independent, pragmatic, randomised controlled trials. *BMJ.* 2022;379:e072007.
147. Tang TS, Bieber T, Williams HC. Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful? *JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY.* 2014;133:1615-+.
148. Lax SJ, Harvey J, Axon E, Howells L, Santer M, Ridd MJ, et al. Strategies for using topical corticosteroids in children and adults with eczema. *Cochrane Database of Systematic Reviews.* 2022;2022:CD013356.
149. Greiwe J, Honsinger R, Hvisdas C, Chu DK, Lang DM, Nicklas R, et al. Boxed Warnings and Off-Label Use of Allergy Medications: Risks, Benefits, and Shared Decision Making. *Journal of Allergy and Clinical Immunology: In Practice.* 2022;10:3057-3063.
150. Bashyam AM, Cuellar-Barboza A, Masicampo EJ, Feldman SR. Framing atopic dermatitis topical medication application site discomfort as a signal of efficacy improves willingness to continue use. *J Am Acad Dermatol.* 2020;83:1773-1775.
151. Drugs for Atopic Dermatitis. *JAMA.* 2021;325:1321-1322.
152. Drugs for atopic dermatitis. *Med Lett Drugs Ther.* 2020;62:89-96.

153. Nicol NH, Boguniewicz M, Strand M, Klinnert MD. Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program. *J Allergy Clin Immunol Pract.* 2014;2:400-406.
154. Nicol NH, Boguniewicz M. Wet Wrap Therapy in Moderate to Severe Atopic Dermatitis. *Immunol Allergy Clin North Am.* 2017;37:123-139.
155. National Eczema Association. Wet Wrap Therapy. Vol 2023: National Eczema Association; 2017.
156. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LF, Forman SB, et al. Long-term safety and disease control with ruxolitinib cream in atopic dermatitis: Results from two phase 3 studies. *J Am Acad Dermatol.* 2023;88:1008-1016.
157. Gong X, Chen X, Kuligowski ME, Liu X, Liu X, Cimino E, et al. Pharmacokinetics of Ruxolitinib in Patients with Atopic Dermatitis Treated With Ruxolitinib Cream: Data from Phase II and III Studies. *Am J Clin Dermatol.* 2021;22:555-566.
158. Bissonnette R, Call RS, Raoof T, Zhu Z, Yeleswaram S, Gong X, et al. A Maximum-Use Trial of Ruxolitinib Cream in Adolescents and Adults with Atopic Dermatitis. *American Journal of Clinical Dermatology.* 2022;23:355-364.
159. Leung DYM, Paller AS, Zaenglein AL, Tom WL, Ong PY, Venturanza ME, et al. Safety, pharmacokinetics, and efficacy of ruxolitinib cream in children and adolescents with atopic dermatitis. *Annals of Allergy, Asthma & Immunology.* 2022.
160. Johansson M, Guyatt G, Montori V. Guidelines should consider clinicians' time needed to treat. *BMJ.* 2023;380:e072953.
161. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJC, Gorbach SL, et al. Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections: 2014 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases.* 2014;59:e10-e52.
162. Francis NA, Ridd MJ, Thomas-Jones E, Butler CC, Hood K, Shepherd V, et al. Oral and Topical Antibiotics for Clinically Infected Eczema in Children: A Pragmatic Randomized Controlled Trial in Ambulatory Care. *Ann Fam Med.* 2017;15:124-130.
163. Francis NA, Ridd MJ, Thomas-Jones E, Shepherd V, Butler CC, Hood K, et al. A randomised placebo-controlled trial of oral and topical antibiotics for children with clinically infected eczema in the community: the ChildRen with Eczema, Antibiotic Management (CREAM) study. *Health Technol Assess.* 2016;20:i-xxiv, 1-84.
164. Dhar S, Kanwar AJ, Kaur S, Sharma P, Ganguly NK. Role of bacterial flora in the pathogenesis & management of atopic dermatitis. *Indian J Med Res.* 1992;95:234-238.
165. Boguniewicz M, Sampson H, Leung SB, Harbeck R, Leung DY. Effects of cefuroxime axetil on Staphylococcus aureus colonization and superantigen production in atopic dermatitis. *J Allergy Clin Immunol.* 2001;108:651-652.
166. Ewing CI, Ashcroft C, Gibbs AC, Jones GA, Connor PJ, David TJ. Flucloxacillin in the treatment of atopic dermatitis. *Br J Dermatol.* 1998;138:1022-1029.
167. George SMC, Karanovic S, Harrison DA, Rani A, Birnie AJ, Bath-Hextall FJ, et al. Interventions to reduce Staphylococcus aureus in the management of eczema. *Cochrane Database of Systematic Reviews.* 2019;CD003871.
168. Ong PY, Boguniewicz J, Chu DK. Skin Antiseptics for Atopic Dermatitis: Dissecting Facts From Fiction. *The Journal of Allergy and Clinical Immunology: In Practice.*
169. World Health Organization (WHO). Antimicrobial resistance. Vol 2023: World Health Organization (WHO); 2021.
170. United Nations (UN). Antimicrobial resistance: a global threat. Vol 2023: United Nations; 2022.
171. Huang JT, Abrams M, Tlougan B, Rademaker A, Paller AS. Treatment of Staphylococcus aureus colonization in atopic dermatitis decreases disease severity. *Pediatrics.* 2009;123:e808-814.
172. Sawada Y, Tong Y, Barangi M, Hata T, Williams MR, Nakatsuji T, et al. Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro. *J Allergy Clin Immunol.* 2019;143:1946-1948.

173. Keet C, Pistiner M, Plesa M, Szelag D, Shreffler W, Wood R, et al. Age and eczema severity, but not family history, are major risk factors for peanut allergy in infancy. *Journal of Allergy and Clinical Immunology.* 2021;147:984-991.e985.
174. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy--randomized trials in individual patients. *N Engl J Med.* 1986;314:889-892.
175. Guyatt G, Sackett D, Adachi J, Roberts R, Chong J, Rosenbloom D, et al. A clinician's guide for conducting randomized trials in individual patients. *Cmaj.* 1988;139:497-503.
176. Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol.* 1999;104:466-472.
177. Werfel T, Ahlers G, Schmidt P, Boeker M, Kapp A, Neumann C. Milk-responsive atopic dermatitis is associated with a casein-specific lymphocyte response in adolescent and adult patients. *J Allergy Clin Immunol.* 1997;99:124-133.
178. Abernathy-Carver KJ, Sampson HA, Picker LJ, Leung DY. Milk-induced eczema is associated with the expansion of T cells expressing cutaneous lymphocyte antigen. *J Clin Invest.* 1995;95:913-918.
179. Campana R, Mothes N, Rauter I, Vrtala S, Reininger R, Focke-Tejkl M, et al. Non-IgE-mediated chronic allergic skin inflammation revealed with rBet v 1 fragments. *J Allergy Clin Immunol.* 2008;121:528-530 e521.
180. Wilcock LK, Francis JN, Durham SR. IgE-Facilitated Antigen Presentation: Role in Allergy and the Influence of Allergen Immunotherapy. *Immunology and Allergy Clinics.* 2006;26:333-347.
181. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* 2011;127:S1-55.
182. Lechner A, Henkel FDR, Hartung F, Bohnacker S, Alessandrini F, Gubernatorova EO, et al. Macrophages acquire a TNF-dependent inflammatory memory in allergic asthma. *J Allergy Clin Immunol.* 2021;149:2078-2090.
183. Kita H. How are airborne allergens remembered by the immune system? *J Allergy Clin Immunol.* 2022;149:1940-1942.
184. Chevigne A, Jacquet A. Emerging roles of the protease allergen Der p 1 in house dust mite-induced airway inflammation. *J Allergy Clin Immunol.* 2018;142:398-400.
185. Cho HJ, Lee HJ, Kim SC, Kim K, Kim YS, Kim CH, et al. Protease-activated receptor 2-dependent fluid secretion from airway submucosal glands by house dust mite extract. *J Allergy Clin Immunol.* 2012;129:529-535, 535 e521-525.
186. Fukunaga M, Gon Y, Nunomura S, Inoue T, Yoshioka M, Hashimoto S, et al. Protease-mediated house dust mite allergen-induced reactive oxygen species production by neutrophils. *Int Arch Allergy Immunol.* 2011;155 Suppl 1:104-109.
187. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat Med.* 2009;15:410-416.
188. Kim DH, Choi E, Lee JS, Lee NR, Baek SY, Gu A, et al. House Dust Mite Allergen Regulates Constitutive Apoptosis of Normal and Asthmatic Neutrophils via Toll-Like Receptor 4. *PLoS One.* 2015;10:e0125983.
189. Marschall P, Wei R, Segaud J, Yao W, Hener P, German BF, et al. Dual function of Langerhans cells in skin TSLP-promoted TFH differentiation in mouse atopic dermatitis. *J Allergy Clin Immunol.* 2021;147:1778-1794.
190. Nygaard U, Hvid M, Johansen C, Buchner M, Folster-Holst R, Deleuran M, et al. TSLP, IL-31, IL-33 and sST2 are new biomarkers in endophenotypic profiling of adult and childhood atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2016;30:1930-1938.
191. Traidl S, Werfel T. [Allergen immunotherapy for atopic dermatitis]. *Hautarzt.* 2021;72:1103-1112.

192. Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. *J Allergy Clin Immunol.* 2017;140:1485-1498.
193. Caminiti L, Panasiti I, Landi M, De Filippo M, Olcese R, Ciprandi G, et al. Allergen immunotherapy in atopic dermatitis: Light and shadow in children. *Pediatr Allergy Immunol.* 2020;31 Suppl 26:46-48.
194. Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. *Immunity.* 2021;54:291-307.e297.
195. Beck LA, Bissonnette R, Deleuran M, Nakahara T, Galus R, Khokhar FA, et al. 417 Safety of long-term dupilumab treatment in adults with moderate-to-severe atopic dermatitis: results from an open-label extension trial up to 5 years. *British Journal of Dermatology.* 2023;188.
196. Beck LA, Deleuran M, Bissonnette R, de Bruin-Weller M, Galus R, Nakahara T, et al. Dupilumab Provides Acceptable Safety and Sustained Efficacy for up to 4 Years in an Open-Label Study of Adults with Moderate-to-Severe Atopic Dermatitis. *Am J Clin Dermatol.* 2022;23:393-408.
197. Oykhman P, Paramo FA, Bousquet J, Kennedy DW, Brignardello-Petersen R, Chu DK. Comparative efficacy and safety of monoclonal antibodies and aspirin desensitization for chronic rhinosinusitis with nasal polyposis: A systematic review and network meta-analysis. *Journal of Allergy and Clinical Immunology.* 2022;149:1286-1295.
198. Rank MA, Chu DK, Bognanni A, Oykhman P, Bernstein JA, Ellis AK, et al. The Joint Task Force on Practice Parameters GRADE guidelines for the medical management of chronic rhinosinusitis with nasal polyposis. *Journal of Allergy and Clinical Immunology.* 2023;151:386-398.
199. Agnihotri G, Shi K, Lio PA. A Clinician's Guide to the Recognition and Management of Dupilumab-Associated Conjunctivitis. *Drugs in R&D.* 2019;19:311-318.
200. McMurtry CM, Taddio A, Noel M, Antony MM, Chambers CT, Asmundson GJ, et al. Exposure-based Interventions for the management of individuals with high levels of needle fear across the lifespan: a clinical practice guideline and call for further research. *Cogn Behav Ther.* 2016;45:217-235.
201. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *New England Journal of Medicine.* 2022;386:316-326.
202. Molander V, Bower H, Frisell T, Delcoigne B, Di Giuseppe D, Askling J. Venous thromboembolism with JAK inhibitors and other immune-modulatory drugs: a Swedish comparative safety study among patients with rheumatoid arthritis. *Annals of the Rheumatic Diseases.* 2023;82:189.
203. Burmester GR, Cohen SB, Winthrop KL, Nash P, Irvine AD, Deodhar A, et al. Safety profile of upadacitinib over 15 000 patient-years across rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis and atopic dermatitis. *RMD Open.* 2023;9.
204. Three drugs for atopic dermatitis (Adbry, Cibinqo, and Rinvoq). *Med Lett Drugs Ther.* 2023;65:51-55.
205. Tran KB, Lang JJ, Compton K, Xu R, Acheson AR, Henrikson HJ, et al. The global burden of cancer attributable to risk factors, 2010–19: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet.* 2022;400:563-591.
206. National Cancer Institute. Cancer in Children and Adolescents. Vol 2023: NIH National Cancer Institute; 2021.
207. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Advances.* 2018;2:3198-3225.

208. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart Disease and Stroke Statistics—2022 Update: A Report From the American Heart Association. *Circulation.* 2022;145:e153-e639.
209. Sbidian E, Chaimani A, Garcia-Doval I, Doney L, Dressler C, Hua C, et al. Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis. *Cochrane Database Syst Rev.* 2022;5:Cd011535.
210. Dantal J, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, et al. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *The Lancet.* 1998;351:623-628.
211. Zurbriggen B, Wuthrich B, Cachelin AB, Wili PB, Kagi MK. Comparison of two formulations of cyclosporin A in the treatment of severe atopic dermatitis. A double-blind, single-centre, cross-over pilot study. *Dermatology.* 1999;198 (1):56-60.
212. Elder CA, Moore M, Chang C-T, Jin J, Charnick S, Nedelman J, et al. Efficacy and Pharmacokinetics of Two Formulations of Cyclosporine A in Patients with Psoriasis. *The Journal of Clinical Pharmacology.* 1995;35:865-875.
213. Anderson IF, Helve T, Hannonen P, Leirisalo-Repo M, Gilboe IM, Nissilä M, et al. Conversion of patients with rheumatoid arthritis from the conventional to a microemulsion formulation of cyclosporine: a double blind comparison to screen for differences in safety, efficacy, and pharmacokinetics. *J Rheumatol.* 1999;26:556-562.
214. Yocum DE, Allard S, Cohen SB, Emery P, Flipo RM, Goobar J, et al. Microemulsion formulation of cyclosporin (Sandimmun Neoral) vs Sandimmun: comparative safety, tolerability and efficacy in severe active rheumatoid arthritis. On behalf of the OLR 302 Study Group. *Rheumatology (Oxford).* 2000;39:156-164.
215. Otto MG, Mayer AD, Clavien PA, Cavallari A, Gunawardena KA, Mueller EA. Randomized trial of cyclosporine microemulsion (neoral) versus conventional cyclosporine in liver transplantation: MILTON study. Multicentre International Study in Liver Transplantation of Neoral. *Transplantation.* 1998;66:1632-1640.
216. Keown P, Niese D. Cyclosporine microemulsion increases drug exposure and reduces acute rejection without incremental toxicity in de novo renal transplantation. International Sandimmun Neoral Study Group. *Kidney Int.* 1998;54:938-944.
217. Frei UA, Neumayer HH, Buchholz B, Niese D, Mueller EA. Randomized, double-blind, one-year study of the safety and tolerability of cyclosporine microemulsion compared with conventional cyclosporine in renal transplant patients. International Sandimmun Neoral Study Group. *Transplantation.* 1998;65:1455-1460.
218. Brennan DC, Barbeito R, Burke J, Brayman K, Greenstein S, Chang T. Safety of Neoral conversion in maintenance renal transplant patients: A one-year, double-blind study. NOVARTIS OLN-353 Study Group. *Kidney Int.* 1999;56:685-691.
219. Pollard SG, Lear PA, Ready AR, Moore RH, Johnson RW. Comparison of microemulsion and conventional formulations of cyclosporine A in preventing acute rejection in de novo kidney transplant patients. The U.K. Neoral Renal Study Group. *Transplantation.* 1999;68:1325-1331.
220. Cattaneo D, Perico N, Remuzzi G. Generic cyclosporine formulations: more open questions than answers. *Transpl Int.* 2005;18:371-378.
221. Atakan N, Erdem C. The efficacy, tolerability and safety of a new oral formulation of Sandimmun--Sandimmun Neoral in severe refractory atopic dermatitis. *J Eur Acad Dermatol Venereol.* 1998;11:240-246.
222. Chawla M, Ali M, Marks R. Comparison of the steady state pharmacokinetics of two formulations of cyclosporin in patients with atopic dermatitis*. *British Journal of Dermatology.* 1996;135:9-14.
223. Bourke JF, Berth-Jones J, Holder J, Graham-Brown RA. A new microemulsion formulation of cyclosporin (Neoral) is effective in the treatment of cyclosporin-resistant dermatoses. *Br J Dermatol.* 1996;134:777-779.

224. Erkko P, Granlund H, Nuutinen M, Reitamo S. Comparison of cyclosporin A pharmacokinetics of a new microemulsion formulation and standard oral preparation in patients with psoriasis. *Br J Dermatol.* 1997;136:82-88.
225. Gulliver WP, Murphy GF, Hannaford VA, Primmett DR. Increased bioavailability and improved efficacy, in severe psoriasis, of a new microemulsion formulation of cyclosporin. *Br J Dermatol.* 1996;135 Suppl 48:35-39.
226. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. *New England Journal of Medicine.* 2018;380:752-762.
227. Mazaud C, Fardet L. Relative risk of and determinants for adverse events of methotrexate prescribed at a low dose: a systematic review and meta-analysis of randomized placebo-controlled trials. *Br J Dermatol.* 2017;177:978-986.
228. Musters AH, Mashayekhi S, Harvey J, Axon E, Lax SJ, Flohr C, et al. Phototherapy for atopic eczema. *COCHRANE DATABASE OF SYSTEMATIC REVIEWS.* 2021;10:CD013870.
229. Weng QY, Buzney E, Joyce C, Mostaghimi A. Distance of travel to phototherapy is associated with early nonadherence: A retrospective cohort study. *J Am Acad Dermatol.* 2016;74:1256-1259.
230. Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ.* 2017;357:j1415.
231. Price D, Castro M, Bourdin A, Fucile S, Altman P. Short-course systemic corticosteroids in asthma: striking the balance between efficacy and safety. *European Respiratory Review.* 2020;29:190151.
232. Bleecker ER, Menzies-Gow AN, Price DB, Bourdin A, Sweet S, Martin AL, et al. Systematic Literature Review of Systemic Corticosteroid Use for Asthma Management. *American Journal of Respiratory and Critical Care Medicine.* 2020;201:276-293.
233. Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS One.* 2017;12:e0170259.
234. Rice JB, White AG, Scarpati LM, Wan G, Nelson WW. Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clin Ther.* 2017;39:2216-2229.
235. Harb H, Chatila TA. Mechanisms of Dupilumab. *Clinical and Experimental Allergy.* 2020;50:5-14.
236. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *The Journal of allergy and clinical immunology.* 2019;143:155-172.
237. Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A, et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *Journal of Allergy and Clinical Immunology.* 2014;134:1293-1300.
238. Popovic B, Breed J, Rees DG, Gardener MJ, Vinall LMK, Kemp B, et al. Structural Characterisation Reveals Mechanism of IL-13-Neutralising Monoclonal Antibody Tralokinumab as Inhibition of Binding to IL-13R alpha 1 and IL-13R alpha 2. *Journal of Molecular Biology.* 2017;429:208-219.
239. O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT Pathway: Impact on Human Disease and Therapeutic Intervention. *Annual Review of Medicine.* 2015;66:311-328.
240. Akdis M, Aab A, Altunbulakli C, Azkur K, Costa RA, Crameri R, et al. Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: Receptors, functions, and roles in diseases. *Journal of Allergy and Clinical Immunology.* 2016;138:984-1010.

241. Nezamololama N, Fieldhouse K, Metzger K, Gooderham M. Emerging systemic JAK inhibitors in the treatment of atopic dermatitis: a review of abrocitinib, baricitinib, and upadacitinib. *Drugs Context.* 2020;9.
242. Elion GB. The purine path to chemotherapy. *Science.* 1989;244:41-47.
243. Matsuda S, Koyasu S. Mechanisms of action of cyclosporine. *Immunopharmacology.* 2000;47:119-125.
244. Khattri S, Shemer A, Rozenblit M, Dhingra N, Czarnowicki T, Finney R, et al. Cyclosporine in patients with atopic dermatitis modulates activated inflammatory pathways and reverses epidermal pathology. *Journal of Allergy and Clinical Immunology.* 2014;133:1626-1634.
245. Zwerner J, Fiorentino D. Mycophenolate mofetil. *Dermatologic Therapy.* 2007;20:229-238.
246. van Gelder T, Hesselink DA. Mycophenolate revisited. *Transplant International.* 2015;28:508-515.
247. Allison AC. Mechanisms of action of mycophenolate mofetil. *Lupus.* 2005;14:2-8.
248. Tintle S, Shemer A, Suárez-Fariñas M, Fujita H, Gilleaudeau P, Sullivan-Whalen M, et al. Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response. *J Allergy Clin Immunol.* 2011;128:583-593.e581-584.
249. Morita A. Ultraviolet (UV) A and (UV) B Phototherapy. In: Krieg T, Bickers DR, Miyachi Y, eds. *Therapy of Skin Diseases: A Worldwide Perspective on Therapeutic Approaches and Their Molecular Basis*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010:87-91.
250. Vieira BL, Lim NR, Lohman ME, Lio PA. Complementary and Alternative Medicine for Atopic Dermatitis: An Evidence-Based Review. *Am J Clin Dermatol.* 2016;17:557-581.
251. Ungar B, Garcet S, Gonzalez J, Dhingra N, Correa da Rosa J, Shemer A, et al. An Integrated Model of Atopic Dermatitis Biomarkers Highlights the Systemic Nature of the Disease. *Journal of Investigative Dermatology.* 2017;137:603-613.
252. Beck LA, Cork MJ, Amagai M, De Benedetto A, Kabashima K, Hamilton JD, et al. Type 2 Inflammation Contributes to Skin Barrier Dysfunction in Atopic Dermatitis. *JID Innovations.* 2022;2:100131.
253. Price KN, Krase JM, Loh TY, Hsiao JL, Shi VY. Racial and ethnic disparities in global atopic dermatitis clinical trials. *Br J Dermatol.* 2020;183:378-380.
254. Sevagamoorthy A, Sockler P, Akoh C, Takeshita J. Racial and ethnic diversity of US participants in clinical trials for acne, atopic dermatitis, and psoriasis: a comprehensive review. *J Dermatolog Treat.* 2022;33:3086-3097.
255. Ding J, Joseph M, Yau N, Khosa F. Underreporting of race and ethnicity in paediatric atopic dermatitis clinical trials: a cross-sectional analysis of demographic reporting and representation. *Br J Dermatol.* 2022;186:357-359.
256. The Journal of Allergy and Clinical Immunology: In Practice. Reporting Race and Ethnicity. Vol 20232023.
257. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated May 2023. ed2023.
258. Fong WCG. Just another eczema case for you, but to me it's the world. *BMJ.* 2021;374:n1531.

Appendix Supplement to the JTF AD Guidelines

Title

Atopic Dermatitis (Eczema) Guidelines: 2023 AAAAI/ACAAI Joint Task Force (JTF) on Practice Parameters GRADE- and Institute of Medicine-based recommendations

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Disclosures

Detailed in the Methods and Appendix, the Guidelines followed JTFPP policies and international standards for addressing potential conflicts of interest. All JTFPP members' COI are available publicly at https://www.allergyparameters.org

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How is a trustworthy guideline made by the AAAAI/ACAAI JTFPP?

The Institute of Medicine laid out how trustworthy guidelines should be made and created key standards as outlined in **Table E1** below. The standards, widely adopted by the international guideline community, are similar to those developed by the Guideline International Network (G-I-N) and McMaster. These guidelines also fulfill requirements for claiming proper use of GRADE[1].

Table E1: Summary of Institute of Medicine standards for trustworthy guidelines and how the JTFPP Atopic Dermatitis guidelines addresses them

1. Establishing transparency ***"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"***
• The guideline methods are available and published with additional details in the supplement. • The guideline and methods are open-access.
2. Managing conflicts of interest ***"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",***
• Interests of each panel member are declared and published with the recommendations. • No one with financial interests in the past two years - as judged by the panel chairs - participated in formulating or drafting recommendations. • Intellectual conflict of interests follow the same standards as financial conflicts of interest. Such conflicts include having taken a strong position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study on the topic. • The co-chairs had methods expertise, a clinical background, and addressed by recusal any financial or intellectual interests declared. If a potential conflict arose, then the chair was recused for that recommendation and was replaced by the methods resource person (GG) for the time required. • Pharmaceutical companies had no role in these recommendations.
3. Guideline Development Group Composition ***"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"***
• The panel sought equity, diversity and inclusiveness through public calls for patient and healthcare provider engagement, gender and age balance, representation from most geographic regions, balance of tertiary care, community, and rural representation, and inclusion of multiple stakeholders (front-line clinicians [pediatricians, family physicians, nurses, pharmacists], patient and caregiver partners, patient advocacy groups, allergists/immunologists and dermatologists, methodologists). • The panel facilitated patient and public involvement by including patient experience, via patient and family partners and systematic reviews on values and preferences to guide outcome choices and the relative importance of each outcome. • Patient and family partners were given priority during panel meetings and had an explicit role in vetting final values and preferences judgements.
4. Clinical Practice Guideline–Systematic Review Intersection ***"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes"***
• Each recommendation is based on one or more high-quality systematic reviews (SRs) developed and published in parallel with, or in advance of, the JTFPP AD Guidelines. • The guideline panel and systematic review teams interacted to facilitate communication and continuity in the process.
5. Establishing Evidence Foundations for and Rating Strength of Recommendations ***"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"***

- The GRADE approach provided the framework for establishing evidence foundations and rating strength of recommendations. For each recommendation, systematic and transparent assessments were made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes of a particular action through structured evidence summaries (e.g. GRADE Summary of Findings tables)
  - Certainty (quality) of the evidence
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome included an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings-tables. If such data were not available, narrative summaries were provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) is available and expanded on in the supplement. This summary includes descriptions of how theory (e.g. pathophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations were rated either weak/conditional or strong, as defined by GRADE.
- If the panel members disagreed on evidence assessment or strength of recommendations, the panel planned to follow a structured consensus process customized to the GRADE system and planned to report any final differences in opinion, with their rationale, in the online supplement. However, the panel reached consensus on all recommendations.

6. Articulation of recommendations
"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation appears in the infographic in the JTFPP Atopic Dermatitis guidelines and are available in standardized formats in the main text, articulated to be actionable based on best current evidence on presentation formats of guidelines.
- There is a statement included in each summary article in the Journal that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualized in the healthcare system a clinician works in, and/or with an individual patient.

7. External review
"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for comment.."

- At least two external peer-reviewers reviewed the guideline for the Journal and provided peer review. Each had access to all the information in the guideline package. Each systematic review followed standard peer-review policies and processes.
- The guideline was posted for public comment and feedback incorporated.
- The JTFPP, with methodological and content expertise, reviewed the Guideline publication and the systematic reviews.
- The JTFPP guideline panel was asked to read and respond to the peer-review comments and make amendments where they judge reasonable

8. Updating
"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The JTFPP monitors each guideline and provides scheduled updates in situations where the evidence suggests a change in practice.
- This JTFPP guidance represents living guidance, with a commitment to publish updated recommendations based on new and practice-changing evidence emerging after the first recommendations are published. The systematic review and meta-analyses produced by the Evidence in Allergy Group may be re-commissioned by the AAAAI/ACAAI to trigger evidence synthesis and rapid development of new or updated recommendations on a systematic basis according to need arising in the global community.

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Addressing potential conflicts of interest

Disclosures

All panel members completed JTFPP and World Health Organization disclosure forms for financial and intellectual conflict of interests. These forms were reviewed by the guideline co-chairs. Any disclosed conflicts were assessed and managed according to JTFPP policies. EIA collaborators also assess and manage disclosures according to their established criteria by the high standards of JTFPP and similar guideline efforts (eg. BMJ Rapid Recommendations).

Those with relevant conflicts of interest to the guideline question participated in the discussion about the scientific evidence and practical issues or implementation considerations and avoided giving judgmental statements that would suggest a specific direction or strength of recommendation during the discussions. They also recused themselves from the formal development of strength and direction of recommendations. Those without potential conflicts drafted the wording of the guideline recommendations. All panel members then provided input on the guideline in its entirety and its corresponding revisions. During revisions, the guideline panel did not change the population, intervention or comparator the recommendation addressed, the strength of recommendation, or its direction. All panel members and the JTFPP approved the final guideline.

Recusals for each group of recommendations

COI	Topicals	Diet	Bleach	Immunotherapy	Systemics
Financial	Anna DeBennedeto, Rachel Asiniwasis, Mark Boguniewicz, Peter Lio, Peck Ong, Jonathan Silverberg	Julie Wang	-	Julie Wang	Anna DeBennedeto, Rachel Asiniwasis, Mark Boguniewicz, Peter Lio, Peck Ong, Lynda Schneider, Jonathan Silverberg, Jonathan Spergel
Intellectual	-	Lynda Schneider, Peter Lio, Julie Wang	-	Matthew Greenhawt	-

No Evidence in Allergy Group members had relevant conflicts of interests.

Bleach baths - JTF AD Guideline Supplement

Practical information

Dilute bleach bathing should be adjunctive to standard eczema skin care (see **Good Practice Statement**) and should not detract from such fundamental skin care routines.

The primary contraindications for taking bleach baths are:

- Uncontrolled asthma because of the risk of inhalation triggering an asthma exacerbation.
- Contact dermatitis to bleach.

For all patients with AD

- Dilute bleach baths used in the RCTs were around a final concentration of 0.005% (sodium hypochlorite) in lukewarm/tepid water for 10 minutes per bath and done twice per week[2].
- The concentration of liquid bleach can vary. Some example recipes are available, https://nationaleczema.org/wp-content/uploads/2018/03/FactSheet_BleachBath_FINAL.pdf. Typical recipes are as follows:

Bathtub size (approximate volume)	Bleach concentration	Approximate bleach amount
Standard bathtub (40 gallons [180 L])	5 to 6% w/v	Just over half of a cup (150 mL]
	8.25% w/v	Just over a third of a cup (110 mL)
Half-full standard tub (20 gallons [90 L])	5 to 6% w/v	A quarter of a cup (63 mL)
	8.25% w/v	3 tablespoons (45 mL)
Baby or toddler bathtub (4 gallon [18 L]	5 to 6% w/v	1 tablespoon (15 mL]
	8.25% w/v	2 **tea**spoons (10 mL)

- Avoid “splashless, low splash or no splash” bleach or bleach with fragrances/scents and other additives since these additional chemicals may be irritants.
- Add the bleach to the water in the tub and ensure it is well mixed before getting into the tub.
- Dilute bleach bathing is often used in combination with additional treatments such as moisturizers or topical medications rather than a complete replacement for any of them.
- Make sure you store the bleach where children cannot reach it.

To reduce harms of diluted bleach bathing

- Do not use extreme water temperature or apply bleach that has not been diluted directly on the skin.
- After completing the dilute bleach bath, rinse off with lukewarm plain water. The usual skin care routine should then follow.
- Consider having dedicated towels/linens to pat dry off since there may be residual dilute bleach that could discolor any linens or clothing used immediately after exiting the bath.
- Individuals with multiple large open sores (severe excoriations, fissures, cracks) may experience more stinging and burning, which might be unacceptable, when bathing in dilute bleach. Patient partners and clinicians, however, remarked that some patients, even when they had severe eczema and open sores, enjoyed bathing in dilute bleach because it was relieving and effective. Patient perspective may vary and should be a discussion point during shared-decision making.
    - Data from application of topical medications shows that counselling and positive framing of potential sensations, including potentially uncomfortable ones, as “a sign the treatment is working” may increase acceptability over solely informing the potential sensations. This may also be applicable when discussing what to anticipate with dilute bleach baths[3].
- Keep the bathroom well-ventilated, eg. keeping a window open or turning on a fan. Bleach odors/vapors can irritate the nose and lungs. This may be particularly important in those with sensitive airways, eg. asthma.
- Do not use bleach baths immediately after the bathtub being cleaned with an ammonia-based cleaner as this can produce a dangerous airborne gas.

Where dilute bleach bathing is unavailable or undesirable

- Other, less well-studied, forms of the adjunctive dilute bleach bathing include a splash/rinse or spray to be used in the shower. This might be more acceptable to individuals who prefer to not sit

in a bathtub, or for those that do not have access to one. Clinicians suggesting this approach should discuss its indirectness to the evidence derived from bathing in a bathtub only.

When dilute bleach baths may not be a good option

- If dilute bleach bathwater is causing eye, nose, or throat irritation, or asthmatic reactions.
- If the dilute bleach bathwater is being swallowed. This can cause abdominal pain, nausea or vomiting, and, depending on the severity, should trigger urgent/emergent medical attention.
- If there is no response to therapy after 4 weeks.

Implementation practical considerations

- **Emotional well-being:** Adding dilute bleach bathing to one's routine may be a burden, especially if there is minimal benefit, multiple treatments or lifestyle modifications involved, or time restraints/inconvenience. People may also worry that bleach will stain their clothes, or towels.
- **Social life and relationships:** Bleach baths do not stain or discolor the skin. While some patient partners voiced that they thought they might feel self-conscious around others about the possibility of smelling like bleach (similar to a chlorinated swimming pool) following a bath, others and clinical experts shared there is often little to no odor.
- **Physical well-being:** Although dilute bleach is also used to bleach clothing, dilute bleach bathing does not discolor the skin.
- **Pregnancy:** The concentration of dilute bleach baths is generally thought to be safe in pregnancy, but there are no formal and rigorous studies specifically addressing this question.
- **Cost and access:** Bleach baths are low cost and accessible in most homes. It is easy to find a bleach bath recipe and be confident in dilution. This treatment can be easily fit into a regular routine (eg. following bathing schedule). Some use diluted bleach as a body wash or chlorinated swimming pools as a substitute, but how similar these are to dilute bleach baths is uncertain.
- **Travel:** Dilute bleach bathing is likely difficult to do while traveling.

Evaluation

Standard evaluation of treatment response should occur, and bleach baths discontinued upon resolution of moderate-severe AD or at the patient's preference. RCTs used the treatment for 4-16 weeks.

Research needs

Addressing imprecision and risk of bias in estimation of treatment effects (benefits and harms) will require robustly conducted and reported RCTs. Studies of longer duration, eg. 52 weeks, are needed to help address bleach baths as a management strategy and uncommon adverse effects. All trials initially identified as “ongoing” at the time of the systematic review[2] were terminated. The linked systematic review[2] showed a RCT of at least 200 participants may be a starting point for addressing these issues.

Future RCTs should focus on patient-important outcomes. Those designing trials might consider the outcomes prioritized by the multistakeholder JTFPP AD Guideline panel and the HOME initiative.

We did not find treatment effect differences in those with or without a history of infection at the time of enrolment in the RCT, as well as in studies that did or did not co-administer antibiotics along with bleach or usual baths. Additional studies are required to better understand whether bleach baths function through their antimicrobial activity (including microbes other than *S. aureus*), direct anti-inflammatory activity, or some combination thereof.

Adaptation

These recommendations are likely applicable to multiple settings, should sufficient water be available.

Summary of Findings – Bleach baths

The findings are detailed in the guideline main text and in the associated systematic review[2].

Dietary elimination - JTF AD Guideline Supplement

Practical information

Shared decision-making, exploring the evidence regarding uncertain small health benefits, potential large (and life-threatening, eg. anaphylaxis) harms, and practical implications of dietary elimination may be optimal for patients to be informed and carefully weigh the treatment approach that best aligns with their values and preferences and to avoid unstructured and unsupervised dietary elimination, if chosen.

Do allergen-specific IgE tests help guide which foods to eliminate?

The systematic review found no difference in the small and uncertain treatment benefits using either an empiric or test-guided approach (skin prick tests or serum allergen-specific IgE). No data substantiate screening using allergy tests for the purposes of food elimination for the treatment of AD and this practice is associated with low yield in finding related potentially allergenic foods. Moreover, it is associated with a high risk of detecting a falsely positive food, where food removal in a sensitized but unexposed infant has been associated with a significantly higher risk of developing IgE-mediated food allergy to that food through avoidance. This effect may be magnified in very young infants.

If pursued, should one or multiple foods be eliminated?

The systematic review identified no difference in the small uncertain benefits to AD severity using elemental diets or eliminating egg alone vs other approaches. Harms likely increase with the number of foods eliminated and the longer the duration of food elimination. The simplest regimen that aligns with patient values and preferences should be pursued.

When dietary elimination may not be a good option

- If dietary elimination caused, or has contributed to, malnutrition or IgE-mediated food allergy
- If the patient has other risk factors for harms such as malnutrition or IgE-mediated food allergy
- If there is no clear and rapid response, or endpoint, to a food elimination trial, as per below

Implementation practical considerations

- **Tests and visits:** Tests do not seem to add to the uncertain small benefits and, may actually mislead: the panel strongly voiced against screening. Safe elimination diets may require additional healthcare visits.
- **Emotional well-being:** Dietary elimination may be difficult for families, especially if multiple individuals have varying dietary needs. It may also be difficult for patients and caregivers to avoid certain foods and carefully monitor their diets. False positive tests can also create additional distress.
- **Pregnancy and nursing:** Added caution should be taken if considered during this period. Patients should see their healthcare provider to discuss specific dietary restrictions and how they may affect nutrition during pregnancy or nursing.
- **Costs and access:** Dietary elimination may be accessible for patients living in areas where a variety of food options and alternatives are available. However, allergen-free foods are more costly in general. See the AAAAI resource regarding food labels, “Food Labels: Read it Before You Eat it!” https://www.aaaai.org/tools-for-the-public/conditions-library/allergies/food-labels
- **Social life and relationships:** Dietary restrictions may affect eating meals with others. This may involve, for instance, identifying allergen-free options at restaurants and social events such as work or school events. Allergen-free spaces may promote adverse social isolation.
- **Travel and driving:** Finding allergen-free foods may be time consuming and it may be tiring or burdensome to constantly monitor diets. This can pose additional stress on patients and caregivers.

Evaluation and possible approaches to reduce harms

If a trial of dietary elimination is strongly being considered, clinicians should provide information on what complete dietary avoidance of a specific allergen entails and have close follow up (eg. within 2-4 weeks, and an example is shown below), especially in infants and young children, to mitigate the risk of promoting IgE-mediated food allergy or malnutrition.

N-of-1 trials may be a objective way to document response with close follow up[4, 5]. Doing so often requires multiple (at least 3) periods of trying the intervention and then the corresponding control and eczema control quantified throughout. For example, measure baseline POEM and SCORAD, followed by 1-2 week(s) of control diet, repeat AD measurements, then 1-2 week(s) of elimination diet, with AD measurements repeated. The more rounds of these periods are done, the stronger the inferences can be made regarding comparisons between the intervention and control periods and therefore, the causal role of the intervention.

Research needs

Limitations of the evidence include that there were few RCTs, the study size was small, and there was a high risk of bias, which precluded moderate or high certainty and precise estimates of effect, and which we addressed using structured GRADE ratings leading to low certainty. The small effects seen imply that a large, well conducted RCT (measuring all relevant patient-important outcomes including harms) or RCTs are required to deliver a definitive answer regarding the precise impact of dietary elimination on AD (at least n = 594).

Future RCTs, which might employ a multiple cross-over design to minimize durations of dietary avoidance, should focus on all patient-important outcomes including harms of malnutrition and food allergy outcomes. Such trials could address the optimal timing of elimination, reintroduction, number or type of allergens eliminated. Those designing trials might benefit from being informed by the outcomes prioritized by the multistakeholder JTFPP AD Guideline panel and the HOME initiative.

Adaptation

These recommendations are likely to be broadly applicable and easily adaptable to multiple settings.

Summary of Findings – Dietary elimination

The findings are detailed in the guideline main text and in the associated systematic review[6].

Allergen Immunotherapy - JTF AD Guideline Supplement

Practical information

Allergen immunotherapy involves repeated administration of small doses of proteins that an individual is allergic to and, in the context of AD or respiratory allergies, may be given subcutaneously (SCIT) or sublingually (SLIT). Resources from the ACAAI (https://acaai.org/allergies/management-treatment/allergy-immunotherapy/), and AAAAI (https://www.aaaai.org/Tools-for-the-Public/Allergy,-Asthma-Immunology-Glossary/Immunotherapy-Defined) summarize the approaches.

What allergens might be relevant to AD?

The systematic review found similar treatment benefits and harms across all studied inhalant (environmental) allergens. Of these, the majority of randomized trials addressed house dust mite (HDM) compared to the fewer that addressed pollens or pet dander. The randomized trials addressed SCIT and SLIT approximately equally and found them to be similarly beneficial. There were no clear treatment differences between studies that addressed multiple allergens versus a single allergen.

To reduce harms of immunotherapy

- Counsel around and consider risk factors that might be associated with harm, such as a history of severe systemic allergic reactions to immunotherapy, uncontrolled asthma, and for SLIT, a history of eosinophilic esophagitis. Beta-blocker or ACE inhibitor use are conventionally thought of as risk factors for poor anaphylaxis outcomes, but recent data suggest this may not be the case.
- Immunotherapy is usually not started in pregnancy or if there is active malignancy or autoimmune disease.
- Detailed guidance appears in the associated practice parameters addressing allergen immunotherapy as well as anaphylaxis (see https://www.allergyparameters.org/).

When allergen immunotherapy may not be a good option

- Lack of clinical correlation to sensitization (eg. pollen sensitization without seasonal variation in AD disease activity, or pet sensitization without exposure)
- If following an immunotherapy schedule is difficult or burdensome to the patient or family.
- If the immunotherapy is causing severe or recurrent adverse effects.
- If there is no clear response to the therapy.

Implementation practical considerations

- **Medication routine:** The first dose of SLIT is usually observed in-clinic and is then self-administered daily thereafter. SCIT usually begins as weekly in-clinic injections for 3-5 months (called the build-up phase since it progresses less concentrated to more concentrated allergen strength per injection), then, once the top dose of the most concentrated allergen vial is reached, switches to monthly in-clinic injections (maintenance phase). Some clinicians instead slowly space out the transition to monthly maintenance injections by doing them every other week, then every third week, then monthly.

  FDA-approved SLIT tablets address only HDM, grass, ragweed, or birch pollen. SCIT can address more allergens.
- **Tests and visits:** SLIT can be done at home. SCIT should be supervised by clinicians. After each injection, patients are monitored for adverse reactions for about 30 minutes.
- **Physical well-being:** For at least two hours after SCIT, it is advised to not undergo heavy physical exertion as this may provoke an allergic reaction.
- **Pregnancy and nursing:** Pregnant patients on stable maintenance doses of SLIT or SCIT are usually thought to be safe to continue immunotherapy, but patients considering this should undergo individualized decision-making with their care providers.
- **Costs and access:** Patients usually find allergen immunotherapy relatively affordable. With SCIT, patients can find it difficult to schedule time away from work or school to attend visits. While SLIT is more expensive, it is self-administered so it does not require office visits to use.

- **Travel and driving:** Office visits can usually be arranged to adjust around travel schedules for SCIT. If doses are missed, make-up doses may have to be done. SLIT is comparatively much easier to travel with.

Evaluation

Evaluation of treatment response should address both skin and, as relevant, respiratory signs and symptoms. The RCTs typically observed immunotherapy to take months to take effect (median 5 months), which aligns with the experience in addressing respiratory allergies.

Research needs

The data are sparse for some outcomes like itch, sleep, and flares. Future studies should ensure that all patient-important outcomes are reported and that when collected, all measures are fully reported. Time-to-effect analyses are crude estimates, and future studies must formally address this. Future studies should clearly document whether systemic reactions after AIT for AD are immediate (eg, anaphylaxis) or delayed (eg, eczematous eruption or AD flare). No study addressed AIT's potential long-term immunomodulatory effects.

Adaptation

These recommendations are likely to be broadly applicable and easily adaptable to multiple settings.

Summary of Findings – Allergen Immunotherapy for Atopic Dermatitis

The findings are detailed in the guideline main text and in the associated systematic review.[7]

Moisturizers - JTF AD Guideline Supplement

Practical information

Purchasing prescription moisturizer devices (eg. Atopiclair, Eletone, Epiceram, MimyX, Neosalus, Zenieva, and PruMyx) from a direct pharmacy may lead to prescription costs being significantly lower, even similar to the cost of over-the-counter moisturizers with the added benefit of insurance absorbing the cost. While this helps address the cost issue, it does not address the other burdens, inconvenience, and certain small benefits and uncertain other benefits and harms.

Implementation practical considerations

Standard application of topical treatments can be facilitated by action plans and education on amounts to apply such as fingertip units (See **Topical Corticosteroids Supplement**), eg. (https://www.dermatoqc.org/sites/prod/files/eczema_guide_clinique_patients_eng_vf.pdf or the ACAAI CREATE Decision Aid).

- **Medication routine:** Moisturizers may be applied before or after other topicals or alone. The optimal timing between application of moisturizers and topical medications is not yet known. Clinical experts suggest about 5-10 minutes between applying topical medications and moisturizers. Patients should maintain consistency and find personal routines that work best for them and adapt as needed. Young children may not be used to applying a moisturizer. Strategies such as having children “help” to rub in small areas or “draw” with moisturizer on the skin can help build comfort.
- **Social life and relationships:** Some people may feel self-conscious about the appearance of thick moisturizers (eg. causing matting of hair or causing it to appear greasy) or prefer lighter options during the day.
- **Costs and access:** Are addressed above.
- **Travel and driving:** During travel, over-the-counter moisturizers are generally easier to obtain compared to prescription moisturizer devices.

Evaluation

Standard follow up and structured AD evaluation after a trial of 2-6 weeks.

Research needs

Definitive multi-arm trials comparing prescription devices along with standard high-quality over-the-counter moisturizers, possibly analogous to a recently published RCT[8], that capture all patient-important outcomes over a year or more could definitively improve decision making in mild-moderate AD. The role of prescription moisturizer devices in moderate-severe AD, either induction, remission, or both, also requires clarity.

Adaptation

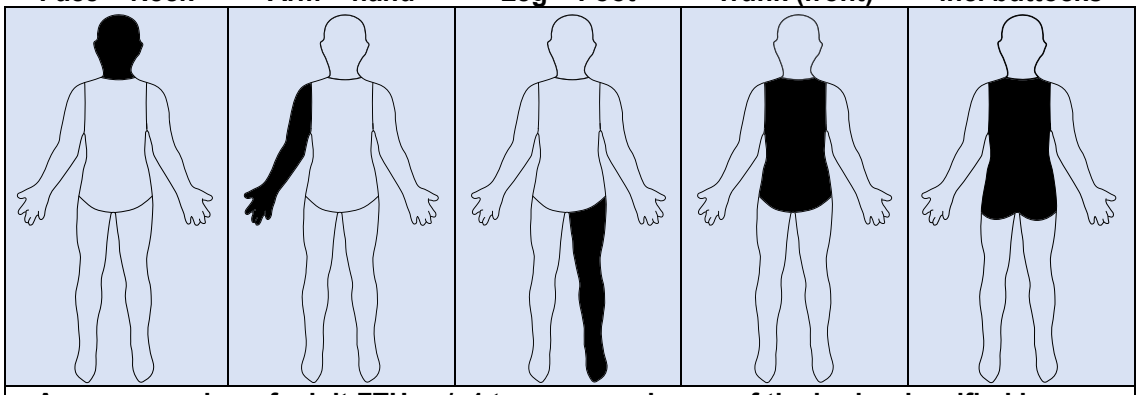
The most common over-the-counter moisturizers and prescription moisturizers may vary by region.

Topical Corticosteroids (TCS) - JTF AD Guideline Supplement

Practical information for applying any topical treatment or moisturizer

The main guideline text and tables address the names and classification of topical treatments for AD.

A **fingertip unit (FTU)** is the amount of ointment squeezed from the index fingertip to its closest crease (distal end of the finger to distal interphalangeal crease). When squeezed from a standard 5 mm diameter tube nozzle, based on sex and gender, 1 FTU covers 2 adult hands with fingers together in area (260-310 cm^2) and uses 0.4-0.5 g of cream/ointment[9-13]. This concept can be helpful when estimating prescription needs and to understand how much topical medication to use.



	Face + Neck	Arm + hand	Leg + Foot	Trunk (front)	Trunk (back) incl buttocks
Age	**Average number of adult FTUs +/- 1 to cover each area of the body, classified by age**				
3-6 months	1	1	1½	1	1½
1-2 years	1½	1½	2	2	3
3-5 years	1½	2	3	3	3½
6-10 years	2	2½	4½	3½	5
12 years	2½	4	7	5	7
Teen/Adult	2½	4	8	7	9

To reduce harms of topical corticosteroids

- Use the lowest potency corticosteroid and for the shortest amount of time required to gain and maintain control of AD.
- Do not use potent topical corticosteroids on sensitive areas (eg. face, folds) for more than 4 weeks consecutively.
- Consider evaluating for contact dermatitis to corticosteroids and excipients in a patient (eg. via patch testing for propylene glycol and considering Coopman classification) with recurrent flares to application sites.

Implementation practical considerations

Topical corticosteroids (TCS) can be applied once or twice per day to gain control of AD flares, ie. induce remission (see the Guideline's corresponding **Recommendation 6**). As per the **Good Practice Statement**, education on treatments, including patient handouts, action plans and amounts to be applied to be effective (eg. explanation and demonstration of fingertip unit) are all components of optimal care.

- **Medication routine:** Topical treatments may take time and involve a trial-and-error process. Topical treatments may come in lotion, foam, cream, and ointment form—each have a place for use and can vary in how messy they are when applied. Patients should maintain consistency and find personal routines that work best for them and adapt as needed.
- In young children, it may also be important to consider if topicals are applied in areas that may be accidently ingested (eg. hands). Distracting young children so they keep their hands out of their mouth immediately after topical medication application will allow time for absorption.

- **Adverse effects:** Prolonged (almost daily) and non-stop use of steroids, especially high-potency ones, may result in rare side effects, such as skin dyspigmentation, stretch marks, formation of small blood vessels (telangiectasia), easy bruising, and persistent redness.
- **Pregnancy and nursing:** Topical corticosteroids, used appropriately, are generally thought to be safe during pregnancy and nursing. TCS should not be applied around the nipples immediately before breastfeeding and might optimally be applied right after a feed is completed.
- **Cost and access:** Prescribing larger sized tubes or tubs may reduce the burden of frequent refills and multiple trips to the pharmacy.
- **Travel and driving:** AD can often flare with travel and it may be helpful to bring medications on trips. Different sized or shaped tubes and containers may be used to transport and store medication when away from home.
- **Social life and relationships, work and education:** Patients may prefer privacy when applying topicals (eg. at home in morning or before bed), rather than applying it publicly or in work or school-related environments, to avoid worrying about staining their clothes or feeling self-conscious.

Evaluation

Standard structured AD assessment should occur in 2-4 weeks.

Research needs

- RCT data robustly addressing sleep disturbance.
- RCTs comparing effectiveness of therapies using TCI versus other topical treatments alone and in combination with them (eg. TCS + TCI) could improve how to optimally use them to treat flares of AD and prevent future ones.
- RCTs reporting location-specific outcomes could help clarify the optimal treatments for sensitive areas (eg. head and neck, genitals, folds) versus the rest of the body.

Adaptation

The worldwide availability of TCS facilitates adaptation.

Summary of Findings – see JTF AD guideline main text for table

Wet wrap (occlusive) therapy - JTF AD Guideline Supplement

Practical information for using wet wrap therapy (WWT)

Online educational resources[14, 15] are available (https://nationaleczema.org/eczema/treatment/wet-wrap-therapy/, https://nationaleczema.org/blog/get-the-facts-wet-wraps/). In-person training and demonstration is likely important to be able to use wet wrap therapy effectively and efficiently. The National Jewish Health Institutional Policy and Procedure, 2008, which may be modified and used for patient care citing National Jewish Health Atopic Dermatitis Program as source, is as follows:

Supplies (NB: Experts recommend using only topical steroids with WWT)

1. Topical moisturizers/medications (eg. triamcinolone 0.1% and desonide 0.05% ointments).
2. Tap water at a comfortably warm temperature.
3. A basin for dampening the dressings.
4. Clean dressings of approximate size to cover the involved area.
    - Face: 2-3 layers of wet clinging gauze bandages held in place with expandable orthopedic or surgical net covering.
    - Arms, legs, hands, and feet: 2-3 layers of wet clinging gauze bandages gauze held in place with elastic bandages or tube socks, or cotton gloves, or wet tube socks, followed by dry tube socks; tube socks may be used for wraps for hands and feet, and larger ones may work as leg and/or arm covers.
    - Total body: combination of above or wet pajamas or long underwear and turtleneck shirts covered by dry pajamas or sweatsuit. Pajamas with feet work well for the outer layer.
5. Blankets to prevent chilling.
6. Nonsterile gloves if desired.

Procedure

1. Be certain that the patient's room is warm and ensure privacy. Gather supplies.
2. If wraps are to be applied to a large portion of the body, work with 2 people if possible. It is necessary to work rapidly to prevent chilling.
3. Explain the procedure to the patient and parent.
4. Fill the basin with warm tap water.
5. The patient will have had a 10-20 min soaking bath in warm water without additional additives before this procedure. Pat skin dry with a towel.
6. Apply the appropriate topical medications to affected areas and moisturizer to nonaffected areas immediately after pat drying the skin. Use clean plastic spoons or tongue depressor to avoid contamination of products in jars. This allows large areas to be covered quickly and prevents caregivers from unnecessary exposure to topical medications.
7. Soak the dressings in very warm water because they cool quickly in this process. Squeeze out excess water. Dressings should be wet, not dripping. As per below, damp clothes can be used.
8. Cover an area with wet dressing chosen for the area and the patient. Immediately after wrapping, cover with appropriate dry material, such as an elastic bandage, socks, or pajamas. Start at the feet and move upward. Use damp long underwear or pajamas (eg. warm rinse cycle in clothes washer) covered by dry pajamas or a sweatsuit with total body involvement in place of wet gauze.
9. Take steps to avoid chilling. A blanket can be put in a dryer to warm it, and cover the patient, but do not overheat the patient. Wraps can be removed after 2-4 hours. A warm blanket and snuggling help pass the time. Wraps may be left on overnight if they are applied at bedtime.
10. If the patient is known or suspected to have an infection of the involved areas, place dressings in the appropriate bag and dispose according to infection control procedure.
11. After all dressings are removed, moisturizers may be applied to the entire body.

To reduce harms of wet wrap therapy

- Use wet wraps on involved areas selectively for areas of more severe eczema, not routinely.
- This should be done under medical supervision for short periods of time (days to 2 weeks).
- Monitor for signs of skin infection.
- Gradually reduce the number of applications of wet wrap therapy according to response to treatment. Large improvements may be seen over roughly four days.
- Skilled nursing techniques are required for use on the face.

When wet wrap therapy may not be a good option

- If wet wrap therapy is too time-consuming or uncomfortable
- Local and systemic corticosteroid adverse effects, contact dermatitis, skin maceration, miliaria, and infections such as folliculitis, impetigo, and herpes.
- Severe AD on face and neck but do not have experienced nursing support to facilitate safe wet wrap therapy there.

Implementation practical considerations

- After applying topical medication and/or and emollient, moisten gauze or cotton clothing with warm water. Squeeze out extra water and wrap this around the affected area. Some families find it easier to wet the clothing using their washing machine, spin on the high setting, and then apply the damp clothing. Follow by applying a dry wrap, or clothes/pajamas. Patients may prefer co-flex as an additional layer between the wet wrap and clothes to prevent cream from seeping through. Cotton mittens may be used for hands.
- Wet wraps are left in place a minimum of 2 hours. Remove the wraps when they dry out. In general, wet wraps are removed after 4 hours. If the patient falls asleep with wet wraps in place, they may be left on overnight. Wraps should never be constrictive. Apply moisturizer to the total body after wet wraps are removed. Topical medications are usually ointments and not diluted or compounded.

- **Medication routine:** WWT is used with topical corticosteroids only.
- **Adverse effects:** Some patients may find them uncomfortable or irritating if too tight, or the temperature is too cold.
- **Physical well-being:** Wet wraps create a physical barrier to soothe skin and prevent scratching, which may help young children and babies sleep at night.
- **Exercise and activities:** Some patients find wet wraps binding or restrictive.
- **Emotional well-being:** Patients who suffer from sleep disturbance and itching may feel soothed by using wet wraps, especially babies and young children.
  Applying wet wraps may also be time consuming and messy. This may negatively contribute to emotional wellbeing, especially for caretakers.
- **Cost and access:** Wet wraps are not costly and do not require a prescription. Many of the materials can be found at home. The procedure requires time, which may make it less feasible.
- **Travel and driving:** Wet wraps can be brought during travel, but will require extra materials in addition to the standard medications and moisturizers.
- **Social life and relationships:** Patients may prefer privacy when applying wet wraps.

Evaluation

Follow-up with structured AD assessment should occur in 1-2 weeks to start, then at standard intervals.

Research needs

- Parallel-design RCTs comparing WWT with topical medications versus without, and no WWT
- RCTs of WWT as an AD management strategy for acute flares over 52 weeks

Adaptation

With the materials for WWT being commonly available, it should be easily adapted across settings.

Summary of Findings – see JTF AD guideline main text for table

Topical calcineurin inhibitors (TCIs) - JTF AD Guideline Supplement

Practical information for using topical calcineurin inhibitors

TCIs include pimecrolimus 1% cream and tacrolimus ointments (0.03% and 0.1%).

Safety of topical calcineurin inhibitors

The linked systematic review and meta-analysis is the first to evaluate all available data addressing TCI and cancer outcomes. Such an association has been well-publicized since their market approval, and due to the FDA decision to require a "black box" warning on the initially approved branded agent. The new meta-analysis showed that TCI use, compared to not using TCIs, is associated with no credible increase in cancer with findings similar among infants, children, adults; mild, moderate and severe disease; sex; and durations of therapy ranging from 3 weeks to 13 years[16]. Product inserts, and continuing education programs for clinicians (e.g., pharmacists, nurses, psychologists, and physicians) should be updated to reflect the higher-certainty that there is no credible association of TCIs with cancer.

Many of the same practical issues presented in the **Topical Corticosteroids - JTF AD Guideline Supplement** also apply to topical calcineurin inhibitors.

Implementation practical considerations

TCI can be applied once or twice per day to gain control of AD flares, ie. induce remission. Per the **Good Practice Statement**, education on treatments, including patient handouts, action plans and amounts to use (eg. explanation and demonstration of fingertip unit) are all components of optimal care.

- **Medication routine:** Topical treatments may take time and involve a trial-and-error process. TCI may come in cream and ointment form.
- **Adverse effects:** Data from application of topical medications shows that counselling and positive framing of potential sensations, including potentially uncomfortable ones, as "a sign the treatment is working" may increase acceptability over solely informing the potential sensations[3].
    - Other options to limit adverse effects include applying TCIs a few minutes after applying a moisturizer, precooling the tube (eg. in the refrigerator) or applying topical corticosteroids for a few days before applying the TCI.
- **Pregnancy and lactation:** While there are little to no formal studies addressing TCI for AD in pregnancy or lactation, the reassuring safety profile and little to no systemic absorption of TCI in AD, and the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine's designation of oral cyclosporine, a related molecule to calcineurin inhibitors, as low-risk[17-19] are reassuring. If used, apply immediately after, not just before, breastfeeding.
- **Food and drink:** TCI may cause local flushing with alcohol (ethanol) ingestion.

Evaluation

Standard structured AD assessment should occur in approximately 2-4 weeks.

Research needs

- RCTs comparing effectiveness of therapies using TCI versus other topical treatments alone and in combination (eg. TCS + TCI) could improve how to use them optimally.
- RCTs reporting location-specific outcomes could help clarify the optimal treatments for specific areas (eg. head and neck, genitals, folds) versus the rest of the body.

Adaptation

The wide availability of TCI facilitates adaptation.

Summary of Findings – see JTF AD guideline main text for table

Once versus twice daily TCS or TCI - JTF AD Guideline Supplement

Practical information

Tailoring frequency of application to patient's values and preferences and empowering them to step up frequency of therapy as needed could help promote self-efficacy.

Many of the same practical issues are presented in the **Topical Corticosteroids - JTF AD Guideline Supplement** and **Topical Calcineurin Inhibitors - JTF AD Guideline Supplement**.

Implementation practical considerations

- **Medication routine:** Applying topicals once per day may be a simpler routine. It may be helpful for patients to establish a routine of applying topicals in the morning and/or at night.
- **Adverse effects:** Applying once per day may also provide reassurance that there is less medication being used and therefore a lower chance of adverse effects.
- **Cost and access:** Applying twice daily may be more costly than applying once daily, as more medication is used.

Evaluation

Standard structured AD assessment should occur in approximately 2-4 weeks.

Research needs

- RCTs addressing other topical treatments, including tacrolimus 0.1% and pimecrolimus 1%, crisaborole (or other PDE4 inhibitors), JAK inhibitors, or other topical treatments alone or in combination with TCS are required to address optimal topical treatment approaches in AD.
- RCTs of short duration (4-6 weeks) can address induction of remission, but studies must be at least close to 1 year duration to adequately capture whether twice versus once daily (or other application frequencies) are optimal as an overall management strategy - arguably the more pragmatic and patient-important question.

Adaptation

The wide availability of TCI facilitates adaptation.

Summary of Findings – see JTF AD guideline main text for table

Crisaborole - JTF AD Guideline Supplement

Practical information for using crisaborole

Crisaborole is a PDE4 inhibitor. Many of the same practical issues presented in the **Topical Corticosteroids - JTF AD Guideline Supplement** also apply to topical crisaborole.

To reduce harms of crisaborole

- 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.

Implementation practical considerations

Per the **Good Practice Statement**, education on treatments, including patient handouts, action plans and amounts to use (eg. explanation and demonstration of finger tip unit) are all components of optimal care.

- **Medication routine:** Topical treatments may take time and involve a trial-and-error process. Topical crisaborole is an ointment.
- **Adverse effects:** Data from application of topical medications shows that counselling and positive framing of potential sensations, including potentially uncomfortable ones, as "a sign the treatment is working" may increase acceptability over solely informing the potential sensations[3].
- **Pregnancy and lactation:** There are little to no formal studies addressing crisaborole or PDE4 inhibitors for AD in pregnancy or lactation. The monograph lists it as being systemically absorbed, and unknown if excreted into human milk. The monograph, however, reports that there were no adverse developmental effects observed with oral administration of crisaborole in pregnant rats and rabbits during organogenesis at doses up to 3 and 2 times, respectively, the maximum recommended human dose.

Evaluation

Standard structured AD assessment should occur in approximately 2-4 weeks.

Research needs

- RCTs comparing effectiveness of therapies using crisaborole versus other topical treatments alone and in combination (eg. TCS + crisaborole) could improve how to use them optimally.
- RCTs reporting location-specific outcomes could help clarify the optimal treatments for specific areas (eg. head and neck, genitals, folds) versus the rest of the body.

Adaptation

Crisaborole is available in North America and a number of other world regions. The European Union withdrew the drug's approval, under the brand name Staquis, in 2022 (https://www.ema.europa.eu/en/medicines/human/EPAR/staquis). The European Medicines Agency reports that Pfizer Europe MA EEIG notified the European Commission of its decision not to market the product in the EU for commercial reasons. The crisaborole formulation marketed in the US (Eucrisa), and most other regions in the world, contains added 0.1% butylated hydroxytoluene (BHT; an antioxidant and preservative excipient used to stabilize skincare products).

Summary of Findings – see JTF AD guideline main text for table

Topical JAK inhibitors - JTF AD Guideline Supplement

Practical information for using JAK inhibitors

While multiple topical JAK inhibitors are in development, ruxolitinib is the only one currently marketed in North America. Another, delgocitinib ointment, is marketed in Japan. Many of the same practical issues presented in the **Topical Corticosteroids - JTF AD Guideline Supplement** also apply here.

Topical JAKs have a **boxed warning (see Oral JAK section)**. Patients and clinicians considering topical ruxolitinib should thoroughly discuss the potential benefits and harms, and establish whether topical ruxolitinib or another topical or systemic therapy optimally aligns with patient values and preferences.

To reduce harms of JAK inhibitors

- See the **Guideline main text** for important conditions to consider and **risk factors** to avoid.
- Topical ruxolitinib is limited to patients aged 12 years or older who are not immunocompromised or immunosuppressed, **applied as a thin layer to a maximum of 20% body surface area**, and in a short-term or non-continuous manner.
  Do not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks.
- 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.

When topical ruxolitinib may not be a good option

- Exposed to tuberculosis or endemic mycoses, or have resided or traveled in endemic areas
- Have chronic or recurrent infections or risk factors for them, or if recurrent herpes reactivation

Implementation practical considerations

Per the **Good Practice Statement**, education on treatments, including patient handouts, action plans and amounts to use (eg. fingertip unit) are all components of optimal care.

- **Medication routine:** Topical treatments may take time and involve a trial-and-error process. Topical ruxolitinib comes in a cream form.
- **Adverse effects:** Though the limited data examining ruxolitinib's safety is so far reassuring, the drug is systematically absorbed and related oral JAK inhibitors are associated with serious adverse effects such as cancer, blood clots (lungs, legs, heart, brain), infections, and death. It is, however, uncertain whether these data should apply to topical ruxolitinib.
  See the associated **oral JAK inhibitors recommendations and supplement** for more details.
- **Pregnancy and lactation:** Due to possible harmful effects, topical ruxolitinib is contraindicated in pregnancy and lactation.
- **Cost and access:** Topical ruxolitinib is among the most expensive topical treatments for AD (thousands of US dollars per tube) and may not be accessible or affordable, even with insurance, by some patients.

Evaluation

- Apart from standard structured AD assessment in approximately 2-4 weeks after initiation of therapy, patients should be longitudinally monitored and counseled for arterial and venous thrombotic events, serious infections, and malignancy (including skin cancer).
- Monitor for signs and symptoms of low platelets, anemia, or neutropenia and monitor CBC as indicated.
- If no response after 8 continuous weeks, re-evaluate and reconsider optimal therapy.

Research needs

- Robust long-term safety studies, preferably large randomized trials, are critically required to evaluate the safety of topical ruxolitinib. The decision thresholds established by this guideline and the associated systematic review[16] could facilitate decisions by industry and policy makers regarding sample size and duration required to deliver practice-changing evidence.

Adaptation

Topical ruxolitinib is available in North America and a number of other world regions. Due to cost, it may be difficult to fully adapt or access in resource limited settings in North America or internationally.

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Topical antibiotics - JTF AD Guideline Supplement

Practical information for using topical antibiotics

Topical antibiotics are sold on their own or pre-mixed in combination with other topical treatments such as topical corticosteroids or topical calcineurin inhibitors. Topical antibiotics include polymyxin B sulfate-bacitracin (Polysporin ointment), Polymyxin B sulfate-gramicidin (Polysporin cream), Poymyxin B sulfate-bacitracin-gramicidin (Polysporin triple ointment), Bacitracin (Bacitin ointment) Mupirocin (Bactroban cream/ointment), Silver sufadiazine (Flamazine cream), Fusidic acid/fusidate sodium (Fucidin cream/ointment), Fusidic acid 2% plus hydrocortisone (Fucidin H), topical tetracycline, topical gentamycin, topical neomycin, triclosan and others. **Topical antibiotics only address skin infections due to bacteria.** The linked systematic review and network meta-analysis, and others[20, 21], found that **topical antibiotics in mildly infected AD (ie. no extensive or rapidly progressive weeping, crusting, pustules or painful skin, or systemic signs such as fever or sepsis) provide little to no added benefit over addressing the underlying skin inflammation in AD with topical corticosteroids or topical calcineurin inhibitors alone** (see **Recommendation 9** of the Guideline).

To reduce harms of topical antibiotics

- See the **Guideline main text** for important conditions to consider.
- Monitor for a rebound flare of eczema that might suggest contact dermatitis to the topical antibiotic. If suspected, patch testing and/or empiric elimination may be helpful.

Implementation practical 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. Per the **Good Practice Statement**, education on treatments, including patient handouts, action plans and amounts to use (eg. fingertip unit) are all components of optimal care.

- **Medication routine:** Topical treatments may take time and involve a trial-and-error process. Topical antibiotics often come in an ointment form.
- **Adverse effects:** Using antibiotics may contribute to antibiotic resistant bacteria, which may affect the patient or those living with, or caring for, the patient. This may mean that when antibiotics are critically required for an infection, the infection will be more difficult to treat or require alternative, potentially more harmful, antibiotics. Many of the topical antibiotics can cause contact dermatitis.
- **Cost and access:** Topical antibiotics or combination products may cost more than using standard topical anti-inflammatories alone (eg. topical corticosteroids).

Evaluation

Standard structured AD assessment should occur in approximately 2-4 weeks.

Research needs

- The skin microbiome (skin flora) is likely an important contributor to AD, and robust future studies, particularly large randomized trials, are needed to test whether biologically plausible hypotheses can translate into clinically relevant therapeutic strategies.

Adaptation

With antimicrobial resistance one of the top global threats identified by the WHO (https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance) and United Nations (https://www.unep.org/explore-topics/chemicals-waste/what-we-do/emerging-issues/antimicrobial-resistance-global-threat), these recommendations should be widely adopted and adapted.

Summary of Findings – see JTF AD guideline main text for table

Biologics - JTF AD Guideline Supplement

Practical information for using biologics - dupilumab and tralokinumab

While there are many biologics being studied for their potential to safely treat AD, the currently licensed drugs are the monoclonal antibodies, dupilumab (Dupixent) and tralokinumab (Adbry; named Adtralza in Canada, the EU and UK). They are approved by the FDA, Health Canada (HC), and in Europe (EMA).

Some practical issues pertaining to oral JAK inhibitors, see each monograph for more details:

Drug (alphabetical order)	Dupilumab	Tralokinum
Brand name	Dupixent	Adbry, Adtralza
AD drug marketing approval	FDA, HC, EMA	FDA, HC, EMA
Boxed warning?	No	No
Age indication	6 months or older	12 years or older
Injection devices available	Pre-filled syringe (6 months or older), or Autoinjector pen (2 years or older)	Pre-filled syringe
Wholesale price per syringe	~$1000 to $2000 USD	~$1000 USD
Possible initial dosing		
5 to <15 kg	200 mg every 4 weeks	Not applicable. Dosing is by age, not weight
15 to <30 kg	300 mg every 4 weeks	
15 to <30 kg	600 mg (2x 300 mg) once, then 300 mg every 4 weeks	
30 to <60 kg	400 mg (2x 200 mg) once, then 200 mg every 4 weeks	600 mg (4x 150 mg) once, then 300 mg (2x 150 mg) every 2 weeks
≥60 kg	600 mg (2x 300 mg) once, then 300 mg every 2 weeks	
Volume administered	300 mg dose = 2 mL 200 mg dose = 1.14 mL 100 mg dose = 0.67 mL	150 mg dose = 1 mL

Patients well-controlled on either biologic may consider decreasing the frequency of injections, though many may find efficacy noticeable worse if frequency is extended beyond every 4 weeks.

To reduce harms of dupilumab or tralokinumab

- See the **Guideline main text** for considerations and approaches to injections or conjunctivitis.

When dupilumab or tralokinumab may not be a good option

- If there is recurrent or severe conjunctivitis, arthritis or arthralgias, or non-AD facial erythema.
- If there is new vasculitis, such as eosinophilic granulomatosis with polyangiitis.
- If there is known untreated helminth infection

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Biologics are administered subcutaneously. The medication may become effective within days to weeks after the first injection. Effectiveness may improve over a year. **See monograph/label** for detailed injection instructions. The first dose will involve injection training.
    - Keep the medication refrigerated. Remove from the fridge 30 to 45 minutes before administration and then use immediately. Do not shake and do not freeze.
      If not refrigerated, at room temperature up to 25°C, it must be used within 14 days.
- **Immunizations:** Non-live vaccines (eg. Tdap and meningococcal polysaccharide) are safe and efficacious with dupilumab or tralokinumab.
    - For live vaccines (eg. MMR, Varivax), complete immunizations before starting if possible. The optimal way to navigate live vaccines while on biologics for AD is not certain. One suggestion is to hold dupilumab for 12 weeks and then wait to restart for 4 weeks after vaccination. Limited available evidence suggests that holding dupilumab for 4 weeks or more before immunization may also lead to safe and effective vaccination.
- **Adverse effects:** Common minor adverse events include inject site discomfort and conjunctivitis.
- **Pregnancy and nursing:** Animal data and limited human data suggest no clear evidence of harm with dupilumab during pregnancy and lactation. The animal and human data addressing tralokinumab are more limited. Patients who become pregnant while on dupilumab or tralokinumab should discuss with their clinicians about whether to continue or stop the biologic.

- **Cost and access:** Biologics are costly and can be difficult to access. Most biologics companies have patient support programs that will facilitate insurance negotiation, medication delivery, and injection training. The drug can be self-administered at home or given in-clinic by clinicians.
- **Coordination of care:** Patients either pick up the medication or have it shipped to their home by specialty pharmacies. Given its high cost and temperature storage needs, it is helpful to plan ahead to retrieve the medication in a timely manner.
- **Travel and driving:** Since biologics are usually stored at around 4°C, some patients adjust their travel schedules to fall around injection dates and avoid travelling with it. Alternatively, patients can travel with dupilumab or tralokinumab in a bag with ice packs and a thermometer, or, if kept at room temperature as per above, can be used within 14 days.

Evaluation

Standard structured AD assessment should occur in approximately 4-12 weeks. Benefits may be seen in days to weeks of starting therapy and tend to reach maximal effect by 16 weeks, though it is possible for continued improvement to occur over 52 weeks. There is no routine laboratory monitoring required.

Research needs

- Well done long-term safety studies for infants and children to further reinforce overall safety are needed.
- Robust investigator-initiated randomized trials of active interventions, including cyclosporine, methotrexate, and light therapy, are critically required to inform optimal care pathways.
- Robust RCTs of combination therapy of dupilumab, or other biologics, as maintenance therapy, with topical or oral JAK inhibitor used as on-demand therapy for flares are also required.

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – see JTF AD guideline main text for table

Oral (Systemic) JAK inhibitors - JTF AD Guideline Supplement

Practical information for using oral JAK inhibitors

Oral JAK inhibitors for AD include, in alphabetical order, abrocitinib (Cibinqo), baricitinib (Olumiant; approved in other countries for AD but not in the USA), and upadacitinib (Rinvoq). All come with a boxed warning[22] about increased risk of serious heart-related events, cancer, blood clots, and death for the treatment of certain chronic inflammatory conditions (https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death, https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death). Health Canada (HC), the European Medicines Agency (EMA), and the UK MHRA issued similar warnings (https://www.gov.uk/drug-safety-update/janus-kinase-jak-inhibitors-new-measures-to-reduce-risks-of-major-cardiovascular-events-malignancy-venous-thromboembolism-serious-infections-and-increased-mortality).

Some practical issues pertaining to oral JAK inhibitors, see each monograph for more details:

Drug (alphabetical order)	Abrocitinib	Baricitinib	Upadacitinib
Brand name	Cibinqo	Olumiant	Rinvoq
AD Drug marketing approval	FDA, HC, EMA	EMA (Not FDA or HC)	FDA, HC, EMA
Boxed warning?	Yes	Yes	Yes
Age indication	≥12 years	≥18 years (EMA, MHRA)	≥12 years and ≥40 kg
Drug interactions	Extensive, use of formal drug-interaction assessment advised		
Drug metabolism (All 3 metabolized by liver)	Lower dose in **CYP2C19 poor metabolizers. Substrate** of CYP2B6 (minor), **CYP2C19 (major), CYP2C9 (major),** CYP3A4 (minor), OAT1/3; **Inhibits** P-gp/ABCB1	**Substrate** of BCRP/ABCG2, **CYP3A4** (minor), **OAT1/3**, P-glycoprotein/ABCB1 (minor);	**Substrate** of CYP2D6 (minor), **CYP3A4 (major); Induces** BCRP/ABCG2, CYP3A4 (weak), OATP1B1/1B3 (SLCO1B1/1B3)
Other food/drug interactions	Antiplatelet agents (eg. aspirin) in first 3 months.	-	Grapefruit (CYP3A4 inhibition can last a week).
Adult half-life elimination	~3 to 5 hours	~12 to 16 hours	~8 to 14 hours
Doses (tablets) available	50, 100, or 200 mg	1, 2 or 4 mg	15, 30, or 45 mg
Wholesale price per pill	~$200 USD	~$100 to $200 USD	~$245 to $490 USD
Doses with best evidence	100 or 200 mg	2 or 4 mg	15 or 30 mg
Doses per day	1	1	1
Adjust dosing if	Renal impairment. Do not use in severe renal or liver disease. If infectious, low blood count, or other complications, hold drug until issue cleared.		

Some of table summarized from UpToDate. Some experts avoid CYP3A4 inhibitors if using any drug.

To reduce harms of oral JAK inhibitors and when oral JAK inhibitors may not be a good option

- See the **Guideline main text** for additional important conditions and risk factors to consider.
- Close monitoring of:
  - CBC for abnormalities in white blood cells, red blood cells, or platelets
  - Renal function
  - Liver enzymes and function
  - Blood lipids and cardiovascular (stroke, heart attack, peripheral arterial disease) risk
  - Venous thrombosis risk
  - Infections, including tuberculosis, hepatitis, herpes, and keeping immunizations updated
  - Cancer (including skin cancer) risk
  - Abdominal/GI symptoms including GI perforation or diverticulitis
  - Any potential surgeries or procedures
  - Plans for pregnancy and (contra)conception
- Patients and all care providers should formally check any new drug or complementary, alternative, or integrative therapy for drug-interactions with the oral JAK inhibitor.
- Dose reduction or pausing if any abnormalities or infections. Promptly treat infections.

- Complete all age-appropriate immunizations before initiating therapy; avoid administration of live vaccines immediately prior to, during, and immediately after therapy.

Implementation practical considerations

Prior to initiating treatment with one of these oral JAK inhibitors, patients should be screened for:

- Latent TB, viral hepatitides, or other potentially serious infections
- Up-to-date vaccinations, including shingles
- Abnormal cell counts and bleeding or clotting disorders or medications that promote either of them (eg. anticoagulants, antiplatelet agents, hormonal contraception)
- Liver disease and abnormal liver enzymes, and kidney disease
- A history of cancer and up to date age-appropriate cancer screening
- A history of arterial (including cardiovascular risk factors) or venous thrombosis
- Pregnancy or breastfeeding
- Diverticular disease or history of bowel perforation
- Potential drug-drug interactions (likely will require a formal drug-drug interaction program)

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Oral JAK inhibitors come as tablets. They may start working within days.
- **Adverse effects:** Common minor adverse events include upper respiratory infections, urinary tract infections, nausea, headache, diarrhea, and acne vulgaris.
- **Social life and relationships:** To reduce risk of infection, patients taking oral JAK inhibitors may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).
- **Pregnancy and nursing:** Due to signals of toxicity, oral JAK inhibitors are contraindicated in pregnancy and nursing.
- **Cost and access:** Oral JAK inhibitors are costly and can be difficult to access.

Evaluation

Standard structured AD assessment should occur in approximately 4-12 weeks. Benefits may be seen with days to weeks of starting therapy and tend to reach maximal effect by 16 weeks.

Routine clinical and laboratory monitoring is required while on these oral JAK inhibitors for:

- Cancer
- Arterial or venous thrombosis (eg. myocardial infarction, stroke, claudication, superficial or deep-vein thrombosis, or pulmonary embolism)
- Serious infection including opportunistic infection (eg. gram-negative sepsis, fungal infections) reactivation of latent infection (eg. zoster, TB, hepatitides), and neutropenia and/or lymphopenia
- Anemia and thrombocytopenia, including bleeding risk in non-compressible sites (eg. intracranial)
- Liver injury and dyslipidemia
- Bowel perforation

Research needs

Robust studies to definitively address the residual uncertainty for harms are required. Industry, the FDA, and others have shown the feasibility of long-term RCTs in RA with other oral JAK inhibitors[23], in AD with TCIs[16], and in asthma with long-acting beta agonists[24]. We favor the latter, a harmonized set of RCTs randomizing 36,010 participants, where, “Safety concerns regarding long-acting β2-agonists (LABAs) in asthma management were initially identified in a large postmarketing trial in which the risk of death was increased. In 2010, the Food and Drug Administration (FDA) mandated that the four companies marketing LABAs for asthma perform prospective, randomized, controlled trials comparing the safety of combination therapy with a LABA plus an inhaled glucocorticoid with that of an inhaled glucocorticoid alone in adolescents (12 to 17 years of age) and adults. In conjunction with the FDA, the manufacturers harmonized their trial methods to allow an independent joint oversight committee to provide a final combined analysis of the four trials.” A combination of this approach - large definitive RCTs - with the framework used to address cancer safety of TCIs[16] could definitively clarify oral JAK inhibitor safety in AD.

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – see JTF AD guideline main text for table

Azathioprine - JTF AD Guideline Supplement

Practical information for using azathioprine

Azathioprine is an immunosuppressant that has long been used to treat rheumatologic and autoimmune conditions (eg. lupus, inflammatory bowel disease), among other conditions, that may be effective for AD.

The drug is processed by the liver before it becomes active. Azathioprine (brand names Imuran and Azasan) reduces the number and activity of immune cells. It may take weeks to months to take effect.

To reduce harms of azathioprine

- See the **Guideline main text** for important conditions to consider.
- Screening for TPMT and/or NUDT15 gene deficiency is often done before starting azathioprine to reduce the risk toxicity (eg. neutropenia).
- During infections, azathioprine may have to be stopped or the dose lowered to avoid the risk of serious or opportunistic infections. Patients should seek prompt care in case of any fever.
- Complete all age-appropriate immunizations before initiating therapy; depending on the dose, avoid administration of live vaccines immediately prior to, during, and immediately after therapy.
- Close monitoring of:
    - Abnormalities in white blood cells, red blood cells, or platelets
    - Liver enzymes and function
    - Immunizations and infections, including hepatitis and EBV
    - Cancer (including skin cancer) risk
    - Any potential surgeries or procedures
    - Plans for pregnancy and (contra)conception. Many guidelines consider this drug low-risk.
- **Drug-interactions** include gout drugs (eg. allopurinol, febuxostat), ACE inhibitors, and warfarin. Formal drug-interaction program checking is advised with any new drug or herbal medication.

When azathioprine may not be a good option

- Patients with TPMT or NUDT15 deficiency
- Severe liver or kidney dysfunction, or low blood counts
- Recurrent or severe infections or pancreatitis

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Azathioprine comes as tablets and is often taken once or twice daily. It is often started gradually and with blood monitoring. Often the drug is started at 25 to 100 mg per day, then, if there is no toxicity, increased in 50 mg increments to a target dose (eg. 1.5 to 3 mg/kg/day taken as a single dose or divided over the day into two equal doses).
  Take with, or after, food to reduce the chance of the drug causing upset stomach.
- **Adverse effects:** Common minor harms include nausea, vomiting, diarrhea, and appetite loss.
- **Pregnancy and lactation:** Though many guidelines addressing azathioprine for other conditions deem it relatively safe to continue in pregnancy and lactation, patients with AD considering becoming, or who are, pregnant should have an individualized discussion with their clinicians.
- **Cost and access:** Azathioprine is among the most affordable systemic treatments for severe AD.
- **Food and drink:** Strictly limit, if not completely avoid, alcohol (ethanol) as this affects the liver.
- **Social life and relationships:** To reduce risk of infection, patients taking azathioprine may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).
- **Travel and driving:** Use high-quality sunscreen (eg. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured AD assessment in approximately 4-12 weeks after initiation of therapy, blood tests (CBC, liver enzymes and function) are often completed every week for 1 month after starting

azathioprine or with any major dose change. Subsequently, CBC +/- liver tests are done every 1-3 months for as long as the patient is taking azathioprine. Some experts also measure metabolites of azathioprine. Patients should be routinely monitored for drug toxicity, serious infections, and malignancy. Once symptom improvement has been achieved, the dose can be reduced gradually in steps to the lowest effective dose.

Research needs

- Robust randomized trials are required to definitively clarify the benefits and harms of azathioprine in AD in comparison to other systemic medications, particularly to dupilumab, tralokinumab and/or lebrikizumab, and additionally, in comparison to the oral JAK inhibitors above in patients refractory to safer systemic agents (any one of dupilumab/tralokinumab/lebrikizumab or narrow-band UVB).

Adaptation

Azathioprine is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – see JTF AD guideline main text for table

Cyclosporine - JTF AD Guideline Supplement

Practical information for using cyclosporine

Cyclosporine is an immunosuppressant that has long been used to treat autoimmune conditions and prevent rejection of organ transplants, among other conditions, that is often effective for AD.

Cyclosporine (brand names Neoral, SandIMMUNE, Gengraf) reduces activity of immune cells. It may take days to weeks to take effect. Modified cyclosporine (microemulsion form; eg. Gengraf and Neoral) may deliver more reliable effects compared to unmodified forms (eg. Sandimmune).

To reduce harms of cyclosporine

- See the **Guideline main text** for important conditions to consider.
- During infections, cyclosporine may have to be stopped or the dose lowered to avoid the risk of serious or opportunistic infections. Patients should seek prompt care in case of any fever.
- Complete all age-appropriate immunizations before initiating therapy; depending on the dose, avoid administration of live vaccines immediately prior to, during, and immediately after therapy.
- Close monitoring of:
    - Blood pressure
    - Abnormalities in white blood cells, red blood cells, or platelets
    - Kidney function and liver enzymes and function, extended electrolytes, urate, blood lipds
    - Immunizations and infections
    - Oral hygiene
    - Cancer (including skin cancer) risk
    - Any potential surgeries or procedures
    - Plans for pregnancy and (contra)conception. Many guidelines consider this drug low-risk.
- **Drug-interactions (CYP3A4 and p-gp/ABCB1)** include grapefruit and macrolide antibiotics. Formal drug-interaction program checking is advised with any new drug or herbal medication.

When cyclosporine may not be a good option

- Severe kidney or liver dysfunction, or low blood counts
- Uncontrolled hypertension or its complications such as stroke (ischemic, hemorrhagic)
- Poorly controlled diabetes
- Recurrent or severe infections
- Current or previous cancer, severe skin sun damage, extensive phototherapy or radiotherapy

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Cyclosporine comes as capsules or a solution and is often taken twice daily. It is dosed by weight, after adjusting for age, height, and gender. While the target dose of 4 to 5 mg/kg/day may be more effective and rapid-acting than lower doses (eg. 2.5 to 3 mg/kg/day), the higher dose also has a higher risk of harms - individualized decision-making is necessary regarding the exact dose to use. Solutions have specific mixing and handling instructions.
- **Adverse effects:** Common minor adverse events include upset stomach, high blood pressure, tremor, tingling, headache, increased growth of fine hairs, and tender or swollen gums. Patients taking cyclosporine should routinely measure their blood pressure at home.
- **Physical well-being:** Good oral hygiene is particularly important.
- **Pregnancy and lactation:** Though many guidelines addressing cyclosporine for other conditions deem it relatively safe to continue in pregnancy and lactation, patients with AD considering becoming, or who are, pregnant should have an individualized discussion with their clinicians.
- **Cost and access:** Cyclosporine is among the most affordable systemic treatments for severe AD
- **Food and drink:** Avoid dehydration (eg. drink 1.5 L water per day) to reduce the risk of kidney damage. Avoid **grapefruit** or other CYP3A4 inhibitors.
- **Social life and relationships:** To reduce risk of infection, patients taking cyclosporine may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).

- **Travel and driving:** Use high-quality sunscreen (eg. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured AD assessment in approximately 4-12 weeks after initiation of therapy, blood tests (CBC, creatinine, liver enzymes and function) are often done before starting and then monitored, along with blood pressure, every 2 weeks for the 1-2 months, then every 1-3 months for as long as cyclosporine is being taken. Cyclosporine levels are not routinely measured in the treatment of skin conditions, but may be considered in select scenarios (eg. medication changes, drug-interactions, compliance). Patients should routinely monitor for high blood pressure, serious infections, and malignancy.

Once symptom improvement has been achieved, the dose can be reduced gradually in steps (generally by 0.5 to 1 mg/kg) to the lowest effective dose. To mitigate the risk of side effects, treatment is ideally limited to ≤16 weeks at a time, and long-term strategies for safer maintenance therapy should be considered. Clinical experts tend to use of cyclosporine for a maximum of 1 or 2 years due to concerns about promoting cancer with long-term use.

Research needs

- Robust RCTs, both short (eg. 16 weeks) and long-term (eg. 52 or longer weeks), and in particular, in comparison to dupilumab, tralokinumab, and/or JAK inhibitors are critically required to better inform its benefits and harms and optimal place in AD care.

Adaptation

Cyclosporine is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – see JTF AD guideline main text for table

Methotrexate - JTF AD Guideline Supplement

Practical information for using methotrexate

Methotrexate is an antiproliferative and immunosuppressant that has long been used to treat autoimmune conditions and cancer, among other conditions, which may be effective for AD. It may take weeks to months to take effect. It is often taken along with folic acid.

To reduce harms of methotrexate

- See the **Guideline main text** for important conditions to consider.
- During infections, methotrexate may have to be stopped or the dose lowered to avoid the risk of serious or opportunistic infections. Patients should seek prompt care in case of any fever.
- Complete all age-appropriate immunizations before initiating therapy; depending on the dose, avoid administration of live vaccines immediately prior to, during, and immediately after therapy.
- Close monitoring of:
    - Abnormalities in white blood cells, red blood cells, or platelets
    - Mouth lesions and GI adverse effects
    - Kidney function and liver enzymes and function
    - Lung health (which may include chest x-rays)
    - Immunizations and infections (including prescreening for tuberculosis before starting)
    - Cancer (including skin cancer) risk
    - Any potential surgeries or procedures
    - Plans for pregnancy and (contra)conception. This drug is absolutely contraindicated.
- **Drug-interactions** include NSAIDs and sulfa antibiotics. Formal drug-interaction program checking is advised with any new drug or herbal medication.

When methotrexate may not be a good option

- Severe kidney or liver dysfunction, or low blood counts
- If pregnant, breastfeeding, or considering conceiving
- Patients who drink more than 7 alcoholic (ethanol) drinks per week or those that binge drink
- Recurrent or severe infections
- Current or previous cancer

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Methotrexate comes as capsules or a pre-filled injectable syringe (for subcutaneous or intramuscular use) and is often taken **once per week**. On the other days, folic acid is taken instead. The medications must be handled and discarded very carefully. Patients may feel tired or unwell the day of their dosing. Choose a day that is most convenient.
- **Adverse effects:** Common minor adverse events include mouth sores, upset stomach, nausea, vomiting, and feeling unwell or tired for 1-2 days after taking a dose. Hair loss can occur.
- **Physical well-being:** Patients with unexplained new shortness of breath or cough should promptly seek medical attention.
- **Pregnancy and lactation:** Methotrexate is contraindicated in preconception, pregnancy, and lactation. Guidance varies regarding males exposed to methotrexate.
- **Cost and access:** Methotrexate is among the most affordable systemic treatments for severe AD
- **Food and drink:** Strictly limit, if not completely avoid, alcohol (ethanol) as this affects the liver.
- **Social life and relationships:** To reduce risk of infection, patients taking methotrexate may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).
- **Travel and driving:** Use high-quality sunscreen (eg. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured AD assessment in approximately 4-12 weeks after initiation of therapy, blood tests (CBC, creatinine, liver enzymes and function) are often done monitored every 1-2 weeks for

the first month, then every 1-3 months for as long as methotrexate is being taken. Patients should routinely monitor for liver, skin, blood count, and lung, complications, infections, and malignancy. Once symptom improvement has been achieved, the dose can be reduced gradually in steps to the lowest effective dose. Alternative safer long-term strategies for maintenance therapy should be considered.

Research needs

- Robust RCTs, both short (eg. 16 weeks) and long-term (eg. 52 or longer weeks), and in particular, in comparison to dupilumab, tralokinumab, and/or JAK inhibitors or other systemic agents are critically required to better inform its benefits and harms and optimal place in AD care.

Adaptation

Methotrexate is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – see JTF AD guideline main text for table

Mycophenolate - JTF AD Guideline Supplement

Practical information for using mycophenolate

Mycophenolate (mycophenolic acid; Cellcept or Myfortic) is an antiproliferative and immunosuppressant that has long been used to treat autoimmune conditions and organ transplant, among other conditions, which may be effective for AD. It may take weeks to months to take effect.

To reduce harms of mycophenolate

- See the **Guideline main text** for important conditions to consider.
- During infections, mycophenolate may have to be stopped or the dose lowered to avoid the risk of serious or opportunistic infections. Patients should seek prompt care in case of any fever.
- Complete all age-appropriate immunizations before initiating therapy; depending on the dose, avoid administration of live vaccines immediately prior to, during, and immediately after therapy.
- Close monitoring of:
    - Abnormalities in white blood cells, red blood cells, or platelets
    - GI adverse effects
    - Immunizations and infections including hepatitis and tuberculosis
    - Cancer (including skin cancer) risk
    - Any potential surgeries or procedures
    - Plans for pregnancy and (contra)conception. This drug is absolutely contraindicated.
- **Drug-interactions**. Formal drug-interaction program checking is advised with any new drug or herbal medication.

When mycophenolate may not be a good option

- Severe kidney or liver dysfunction, or low blood counts
- If pregnant, breastfeeding, or considering conceiving
- Recurrent or severe infections, or acute inflammatory syndrome (fever, arthralgias, arthritis, myalgias)
- History of gastric or duodenal ulcers, gastrointestinal hemorrhage, and/or perforation
- Uncontrolled blood pressure or diabetes
- Current or previous cancer

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Mycophenolate comes as capsules, tablets, or an oral solution and is often taken twice per day. The medications must be handled with gloves and discarded very carefully. Mycophenolate sodium (Myfortic) and mycophenolate mofetil (CellCept) are **not** interchangeable.
- **Adverse effects:** Common minor adverse events include diarrhea, upset stomach, nausea, vomiting, loss of appetite, edema/swelling, blood pressure changes, insomnia, headache, and feeling unwell or tired.
- **Pregnancy and lactation:** Mycophenolate is contraindicated in preconception, pregnancy, and lactation. Guidance varies regarding males exposed to mycophenolate.
- **Cost and access:** Mycophenolate is among the most affordable systemic treatments for severe AD
- **Food and drink:** Dosing is most consistent when taken on an empty stomach (1 hour before or 2 hour after meals). Strictly limit, if not completely avoid, alcohol (ethanol) as this affects the liver.
- **Social life and relationships:** To reduce risk of infection, patients taking mycophenolate may wish to be particularly mindful about avoiding sick contacts or high-risk situations and following infection prevention measures (masking, hand hygiene, vaccinations).
- **Travel and driving:** Use high-quality sunscreen (eg. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured AD assessment in approximately 4-12 weeks after initiation of therapy, blood tests (CBC, creatinine, liver enzymes and function) are often done monitored every 1-2 weeks for

the first month, then every 1-3 months for as long as mycophenolate is being taken. Patients should routinely monitor for blood count, GI and neurologic complications, infections, and malignancy. Once symptom improvement has been achieved, the dose can be reduced gradually in steps to the lowest effective dose. Alternative safer long-term strategies for maintenance therapy should be considered.

Research needs

- To the extent that mycophenolate is prioritized as an alternative treatment option for severe, refractory AD, robust randomized trials are required to address the existing low and very low certainty evidence and the drugs comparative effectiveness and safety to dupilumab, tralokinumab, and/or JAK inhibitors or other systemic agents.

Adaptation

Mycophenolate is available widely and therefore these recommendations can be adapted in many contexts.

Summary of Findings – see JTF AD guideline main text for table

Narrow-band UVB (NB-UVB) - JTF AD Guideline Supplement

Practical information for using NB-UVB

NB-UVB (TL01) therapy uses 311-313 nm wavelength light to treat various skin conditions and may be effective for AD. It may take days to weeks to take effect. Phototherapy units used to be only available in clinics. Relatively recently, home units have become available. The efficacy and safety of home units, or their comparability to clinic-based phototherapy, is not clear.

To reduce harms of NB-UVB

- See the **Guideline main text** for important conditions to consider.

When NB-UVB may not be a good option

- Recurrent or severe burns
- Light-sensitive conditions
- Cataracts
- Current or previous skin cancer, or risk factors for these (eg. genetic disorders or syndromes)
- Lack of response
- The travel or time required to do NB-UVB is burdensome or otherwise impractical.

Implementation practical considerations

These drugs are combined with topical therapies (**Good Practice Statement)**. Considerations include:

- **Medication routine:** Clinic-based NB-UVB often requires visits 3 times per week.
  Dosing is based on one's skin type (propensity to tan and to burn), and the exact dose that elicits redness or a burn. Doses are then adjusted based on treatment response and adverse effects.
  Each session involves standing in a cabinet with multiple light bulbs/rods in it and can range from less than 5 minutes up to about 30 minutes.
  For treatments, patients often undress and put on UV protective goggles and a face visor. The genitals are covered.
- **Adverse effects:** Common minor adverse events include local redness or burning, pain, itch, tanning, or increased skin dryness. Severe burns, including swelling and blistering, are possible. Cold sores of the lips can be prevented with sun protective lip balm. Premature skin aging and skin cancer are less likely to occur with NB-UVB compared to other UV phototherapies.
- **Pregnancy and lactation:** NB-UVB is often considered safe in pregnancy and lactation. Narrowband UVB can lower folic acid, so pregnant women should discuss folic acid supplementation with their clinicians and individualize discussions about using NB-UVB in pregnancy.
- **Cost and access:** NB-UVB is usually difficult to access due to the time and travel required to attend specific clinics that have phototherapy units. Home therapy units cost in the range of several thousands of US dollars.
- **Travel and driving:** NB-UVB requires additional coordination with travel plans, child care, and work schedules. Between clinic sessions, use high-quality sunscreen (eg. broad spectrum, SPF 30 or higher) and wear UV-protective clothing, headwear, and eyewear to reduce the risk of skin cancer and rash.

Evaluation

Apart from standard structured AD assessment in approximately 4-12 weeks after initiation of therapy, patients should routinely monitor for signs of sun skin damage and skin cancer.

Research needs

- Robust RCTs are required to address the long-term efficacy and safety of NB-UVB in moderate-severe AD refectory to dupilumab or tralokinumab - both home-based and clinic-based NB-UVB and its comparative effectiveness to alternative pharmacotherapies.

Adaptation

The recommendations might be most easily adaptable to high-income countries and settings.

Summary of Findings – see JTF AD guideline main text for table

Systemic (oral) corticosteroids - JTF AD Guideline Supplement

Practical information for using Systemic corticosteroids

Systemic corticosteroids (eg. prednisone, prednisolone, methylprednisolone, and dexamethasone; also called glucocorticoids) are used to treat several conditions, often to address flares of them, and may be effective for AD. It may take days to take effect. **Common problems with systemic corticosteroids are rebound flare of the disease after the drug is stopped, and that there are multiple recognized harms of using long-term or repeated cycles of systemic corticosteroids.**

To reduce harms of Systemic corticosteroids

- For severe or flaring disease, use effective and safer alternative agents instead of high-dose short-term systemic corticosteroids or chronic, even low-dose, systemic steroids.
- Urgently refer to an atopic dermatitis specialist (eg. allergist-immunologist or dermatologist) to facilitate the use of an alternative agent to systemic corticosteroids.

When systemic corticosteroids may not be a good option

- In almost all circumstances, systemic corticosteroids should not be used for patients with atopic dermatitis and instead, safer, more effective, and longer-lasting alternatives used.

Implementation practical considerations

- **Medication routine:** Corticosteroids may come in oral tablets or solutions, or be injected intramuscularly. When given by the oral route they are often limited to a 3 to 5 day course and rebound occurs shortly after, which promote a vicious cycle of recurrent systemic corticosteroid use. With repeated or chronic use, they must be slowly tapered or else life-threatening adverse effects (eg. adrenal crisis) can occur. Such tapers can be complex and unpleasant.
- **Adverse effects:** Common adverse events include face changes and weight gain, growth impairment, increased appetite, diabetes, insomnia, excitability, and possible psychiatric adverse effects such as mania and psychosis. Others include adrenal insufficiency. Less than 30 days of oral steroids, 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)[25]. Harms of repeated or prolonged use include fragility fractures from osteoporosis, cataracts, heart attack/stroke, diabetes, obesity, and bone avascular necrosis.
- **Emotional well-being:** Systemics corticosteroids commonly cause mood changes including not feeling or acting like oneself, mood swings, and irritability (such as anger and impatience).
- **Pregnancy and lactation:** Systemic corticosteroids are often used only if critically indicated during pregnancy and lactation. Systemic corticosteroids may increase the risk of premature rupture of the membranes, intrauterine growth restriction, maternal pregnancy-induced hypertension, gestational diabetes, osteoporosis, and infection.
- **Cost and access:** Although they are usually not financially expensive, systemic corticosteroids are usually only accessible on an urgent or emergent basis, and hence, usually require significant time and travel to attend urgent care clinics, physician offices, or emergency rooms.

Evaluation

Close clinical monitoring and urgent evaluation is required to ensure any rebound can be promptly treated and the patient can transition to a safer long-term control regimen.

Research needs

- Robust RCTs are required to evaluate the efficacy and safety of systemic corticosteroids versus oral JAK inhibitors, or other rapid acting systemic medications, as an intermittent rescue therapy to treat severe flares of AD.

Adaptation

- Systemic corticosteroids are available worldwide, with some evidence suggesting they are overused, and therefore these recommendations should be implemented widely.
- These recommendations also align with recommendations against systemic corticosteroid use in related conditions, such as psoriasis, even in severe flares of the whole body (such as erythroderma).

Summary of Findings – see JTF AD guideline main text for table

References

1. Schünemann HJ, Brennan S, Akl EA, Hultcrantz M, Alonso-Coello P, Xia J, et al. The development methods of official GRADE articles and requirements for claiming the use of GRADE – A statement by the GRADE guidance group. *Journal of Clinical Epidemiology.* 2023;159:79-84.
2. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. *Ann Allergy Asthma Immunol.* 2022;128:660-668.e669.
3. Bashyam AM, Cuellar-Barboza A, Masicampo EJ, Feldman SR. Framing atopic dermatitis topical medication application site discomfort as a signal of efficacy improves willingness to continue use. *J Am Acad Dermatol.* 2020;83:1773-1775.
4. Guyatt G, Sackett D, Adachi J, Roberts R, Chong J, Rosenbloom D, et al. A clinician's guide for conducting randomized trials in individual patients. *Cmaj.* 1988;139:497-503.
5. Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy--randomized trials in individual patients. *N Engl J Med.* 1986;314:889-892.
6. Oykhman P, Dookie J, Al-Rammahy H, de Benedetto A, Asiniwasis RN, LeBovidge J, et al. Dietary Elimination for the Treatment of Atopic Dermatitis: A Systematic Review and Meta-Analysis. *Journal of Allergy and Clinical Immunology: In Practice.* 2022;10:2657-2666.e2658.
7. Yepes-Nuñez JJ, Guyatt GH, Gómez-Escobar LG, Pérez-Herrera LC, Chu AWL, Ceccaci R, et al. Allergen immunotherapy for atopic dermatitis: Systematic review and meta-analysis of benefits and harms. *J Allergy Clin Immunol.* 2023;151:147-158.
8. Ridd MJ, Santer M, MacNeill SJ, Sanderson E, Wells S, Webb D, et al. Effectiveness and safety of lotion, cream, gel, and ointment emollients for childhood eczema: a pragmatic, randomised, phase 4, superiority trial. *The Lancet Child & Adolescent Health.* 2022;6:522-532.
9. Finlay AY, Edwards PH, Harding KG. "Fingertip unit" in dermatology. *Lancet.* 1989;2:155.
10. Long CC, Finlay AY. The finger-tip unit—a new practical measure. *Clinical and Experimental Dermatology.* 1991;16:444-447.
11. Long CC, Finlay AY, Averill RW. The Rule of Hand: 4 Hand Areas=2 FTU=1 g. *Archives of Dermatology.* 1992;128:1129-1130.
12. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *British Journal of Dermatology.* 1998;138:293-296.
13. Bewley A, Dermatol Working G. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *BRITISH JOURNAL OF DERMATOLOGY.* 2008;158:917-920.
14. Nicol NH, Boguniewicz M. Wet Wrap Therapy in Moderate to Severe Atopic Dermatitis. *Immunol Allergy Clin North Am.* 2017;37:123-139.
15. Nicol NH, Boguniewicz M, Strand M, Klinnert MD. Wet wrap therapy in children with moderate to severe atopic dermatitis in a multidisciplinary treatment program. *J Allergy Clin Immunol Pract.* 2014;2:400-406.
16. Devasenapathy N, Chu A, Wong M, Srivastava A, Ceccacci R, Lin C, et al. Cancer risk with topical calcineurin inhibitors, pimecrolimus and tacrolimus, for atopic dermatitis: a systematic review and meta-analysis. *The Lancet Child & Adolescent Health.* 2023;7:13-25.
17. ACOG Committee Opinion No. 776: Immune Modulating Therapies in Pregnancy and Lactation. *Obstet Gynecol.* 2019 (Reaffirmed 2021);133:e287-e295.
18. Silver R, Craigo S, Porter F, Osmundson SS, Kuller JA, Norton ME. Society for Maternal-Fetal Medicine Consult Series #64: Systemic lupus erythematosus in pregnancy. *American Journal of Obstetrics and Gynecology.* 2023;228:B41-B60.
19. Nevers W, Pupco A, Koren G, Bozzo P. Safety of tacrolimus in pregnancy. *Can Fam Physician.* 2014;60:905-906.
20. Tran KW, Mary-Doug. RC0852-000 Topical Antibiotics for Infected Dermatitis: A Review of the Clinical Effectiveness and Guidelines *CADTH rapid response report: summary with critical appraisa*. Ottawa: Canada's Drug and Health Technology Agency; 2017.
21. George SMC, Karanovic S, Harrison DA, Rani A, Birnie AJ, Bath-Hextall FJ, et al. Interventions to reduce Staphylococcus aureus in the management of eczema. *Cochrane Database of Systematic Reviews.* 2019;CD003871.

22. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *New England Journal of Medicine.* 2022;386:316-326.

23. Seymour SM, Lim R, Xia C, Andraca-Carrera E, Chowdhury BA. Inhaled Corticosteroids and LABAs - Removal of the FDA's Boxed Warning. *N Engl J Med.* 2018;378:2461-2463.

24. Greiwe J, Honsinger R, Hvisdas C, Chu DK, Lang DM, Nicklas R, et al. Boxed Warnings and Off-Label Use of Allergy Medications: Risks, Benefits, and Shared Decision Making. *Journal of Allergy and Clinical Immunology: In Practice.* 2022;10:3057-3063.

25. Waljee AK, Rogers MAM, Lin P, Singal AG, Stein JD, Marks RM, et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ.* 2017;357:j1415.

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Fingertip image displaying fingertip units adapted from rocketpixel on Freepik

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Disclosure forms details

Given Name	Surname	Specialty (eg. 'Patient Partner', 'Primary care', 'General Pediatrics', 'Dermatology', 'Allergy/Immunology', 'Psychotherapy', 'Pharmacy', etc.)	Primary affiliation/institution	Job Title	For the preceding 36 months and the next 12 months from today, have you been/will be a member of a board?	What is the name and role of the organization(s)?	What is the type of board? What is the board's role?	How does the interest relate to guideline topic?	Is there a contractual agreement to disseminate product information?	Did/will you receive payment(s)?	Did/will your institution receive payment(s)?
Jonathan	Spergel	Allergy/Immunology	Children's Hospital of Philadelphia	Professor	Yes	Ready Set Food	Advisory Board	Not related	No	Yes	No
Marylaura	Thomas	Caregiver Partner / Chemical Engineering	Arizona State University	Associate Professor	Yes	Sequitur Health Corp.	management board	not applicable. Sequitur Health Corp is a small business that I have co-founded that is doing medical device development for point of care blood sensors for liver disease.	No	Yes	Yes
Jennifer	LeBovidge	Psychology	Boston Children's Hospital	Psychologist	Yes	Asthma and Allergy Association of America, New England Chapter; National Eczema Association	AAFA New England: Board of directors (ongoing), Medical Advisory Committee (ongoing) National Eczema Association (2017-2020): Scientific Advisory Committee	These patient organizations support patients with atopic dermatitis	No	No	No
Katherine Ellison	Mrs.	Parent of patient	None	Assistant Principal	No						
Anna	De Benedetto	Dermatology	University of Rochester Medical center	Associate professor	No						
Peck	Ong	Allergy/Immunology	Division of Clinical Immunology and Allergy, Children's Hospital Los Angeles; Keck School of Medicine, University of Southern California	Associate Professor of Clinical Pediatrics	Yes	Global Parents for Eczema Research	Board of Director; to advise on the mission and goals of the organization	It directly addresses atopic dermatitis	No	Yes	No
Peter	Lio	Dermatology	Northwestern University Feinberg School of Medicine	Clinical Assistant Professor of Dermatology	Yes	National Eczema Association (NEA), a non-profit patient advocacy group	Non-profit patient advocacy group, General Advisory Board	The organization is devoted to atopic dermatitis/eczema	No	No	No
Monica	Oâ€™Brien	Patient Partner	Tufts University School of Medicine	Student	No						
Julie	Wang	Allergy/Immunology	Icahn School of Medicine at Mount Sinai	Professor of Pediatrics	Yes	DBV technologies	advisory board	food allergy	No	Yes	No
Joey	Huynh	Patient partner	Optum	Physical therapist	No						

Rachel N	Asiniwasis	Dermatology	University of Saskatchewan	Dermatologist	Yes	Eczema Society of Canada	Board of Directors	Guidelines are for AD - No financial support (this is a volunteer position with no financial support to date). Peer reviewed content is available on site in a Canadian context, and primary resources such as surveys are done by ESC.	No	No	No
Lynda	Schneider	Allergy/immunology	Boston Children's Hospital	Section Chief, Allergy	Yes	1. Food allergy REsearch and Education Medical Advisory Board 2. Biothea Therapeutics Scientific Advisory Board 3.Syneos for Alladapt Immunotherapeutics data safety monitoring board (DSMB) 4. NIAID DSMB 5. Ukko Scientific Advisory Board	1. medical advisory board - completed 2. scientific advisory board 3. DSMB for OIT product 4. DSMB for NIH funded project 5. scientific	1. no relation 2. no relation 3. no relation 4. no relation 5. no relation	No	Yes	No
Winfred	Frazier	Family Medicine	UPMC St. Margaret Family Medicine Residency Program	Associate Program Director, Medical Director	No						
Mark	Boguniewicz	Allergy/Immunology	National Jewish Health & University of Colorado School of Medicine	Professor	Yes	1. Abbvie 2. Arena 3. Janssen 4. Leo 5. Lilly 6. Pfizer 7. Regeneron 8. Sanofi Genzyme	Advisory boards	Companies are looking to develop or have treatments for atopic dermatitis	No	Yes	No
Kathryn	Wheeler	General Pediatrics	University of Florida	Clinical Assistant Professor	No						
Elaine	Kim	Pharmacy	none (independent consultant)	pharmacist	No						
Jonathan	Silverberg	Dermatology	George Washington University	Associate Professor, Director of Clinical Research, Director of Patch Testing	Yes	Abbvie, Aobiome, Arena, Asana, BioMX, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Novartis, Pfizer, RAPT, Regeneron, Sanofi-Genzyme	Advisory board meetings	related to various therapies in development for atopic dermatitis	No	Yes	No
Matthew	Greenhawt	Allergy	Children's Hospital Colorado	Professor of Pediatrics	Yes	DBV Technologies, Sanofi/Regeneron, Genentech, Nutricia, Novartis, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenis, ALK-Abello, Astra Zeneca, Aravax, and Prota	medical advisory board	The Pfizer board was in June 2020 and was related to the unmet need in eczema care and discussed phase 2 trial data. It was a one time thing and there has been no contact since then. The rest of the work is related to food allergy, asthma, or EoE treatment and not relevant to any atopic dermatitis management or treatment	No	Yes	No
Derek	Chu	Allergy/Immunology	McMaster	Assistant Professor	No						
Gordon	Guyatt	Internal Medicine	McMaster	Professor	No						

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For the preceding 36 months and the next	What is the name and role of the organization(s)?2	What is the nature of the consultancy?	How does the interest relate to guideline topic?3	Is there a contractual agreement to disse	Did/will you receive payment(s)?5	Did/will your institution receive payment

12 months from today, have you had or will you have a consultancy?3						
Yes	Regeneron/Sanofi, produces Dupilumab	Clinical Trial development	Approved medication for Atopic Dermatitis	No	Yes	No
No						
No						
No						
Yes	dMed Biopharmaceutical Co, Ltd	member of independent data monitoring committee	the medication (class) is not on the market yet for AD	Yes	Yes	No
Yes	Sanofi Genzyme and Regeneron, Incyte, Abbvie, Janssen, Pfizer	Advised on development of drugs	the guideline may mention some of these products	No	Yes	No
Yes	Johnson & Johnson, Regeneron/Sanofi Genzyme, AOBiome, Theraplex, Pfizer, La Roche-Posay, L'Oreal, Menlo, AbbVie, Eli LIlly, Unilever, Altus Labs, Dermavant, Micreos, Dermira, Verrica, Amyris, LEO Pharma, Arbonne, Burt's Bees, YobeeCare, Bodewell, Galderam, Kimberly Clark, MyOR Diagnostics, Sonica LLC, ASLAN Pharma, Almirall, Castle Biosciences, Boston Skin Science, Incyte, Sibel Health, Kaleido, Lipidor, Janssen, Concerto Biosciences.	These represent advisory board meetings and more individual consulting relationships with companies focused on dry skin, skin barrier, eczema, atopic dermatitis, and/or itch. There are many products, some still in early phases of development.	All deal with atopic dermatitis or adjacent areas.	No	Yes	No
No						
Yes	ALK Abello Genentech Jubilant Hollister Steir	DMC member Advisory board meeting on food allergy advisory board meeting on allergen extracts	allergy immunotherapy food allergy allergy testing	No	Yes	No
No						
Yes	Leo, Abbvie, Chronicle Companies, Pfizer, L'Oreal, Sanofi, Eli Lilly	Advised on development and clinician input on systemic medications/biologic therapy for psoriasis and atopic dermatitis. For L'Oreal, this was for OTC products for sensitive skin. For Chronicle Companies, I was the co-chair to develop the Indigenous Skin Summit of March 2021.	Guideline will mention medications used by these companies for AD (Pfizer - crisaborole 2%, Leo - Protopic/Elidel, JAK inhibitors and dupilumab/tralokinumab).	No	Yes	Yes
Yes	1. Sanofi Genzyme and Regeneron Pediatric Advisory Board advisory board 2. Leo Pharmaceuticals 3. Amagma Therapeutics 4. DBV Technologies	1. Advise on pediatric atopic dermatitis and use of dupilumab 2. Advise on tralokinumab 3. Teach group about atopic dermatitis 4. Advise on Viaskin peanut patch	1. The guideline will mention a drug produced by this company and others 2. The guideline will mention a drug produced by this company and others 3. The guideline will review questions related to atopic dermatitis management 4. No relation	No	Yes	No
No						
Yes	AbbVie	Advised on immune aspects of atopic dermatitis that can relate to therapeutics	Guidelines will address therapy of atopic dermatitis.	No	Yes	No

No						
Yes	Independent pharmacist consulting services. Currently contractor for McKesson Specialty Pharmacy	Providing pharmacy services by way of checking prescriptions; asking for clarification from health providers when necessary, recommending dose adjustments if appropriate, etc.	Currently I do NOT work with atopic dermatitis related drugs. Some drugs (e.g. Stelara) are used for psoriasis, but not atopic dermatitis as far as I am aware.	No	No	No
Yes	Abbvie, Afyx, Aobiome, Arena, Asana, BioMX, Bluefin, Bodewell, Boehringer-Ingelheim, Celgene, Dermavant, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Incyte, Kiniksa, Leo Pharma, Luna, Menlo, Novartis, Pfizer, RAPT, Regeneron, Sanofi-Genzyme	Consultation related to health outcomes research, trial design, and various medical and commercial aspects of drug development	Related to atopic dermatitis	No	Yes	No
Yes	Aquestive	scientific advisor related to development of an epinephrine sublingual film	not related	No	Yes	No
No						
Yes	UpToDate	Advice on methodology	The guideline also uses GRADE methodology and trustworthy guideline development principles	No	Yes	No

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For the preceding 36 months and the next 12 months from today, has your employer had an interest in the topic covered? You are not required to state any roles you have already mentioned in this statement	What is the name and role of the organization(s)?7	How does the interest relate to guideline topic?8	Is there a contractual agreement to disseminate product information?9	Did/will you receive payment(s)?10	Did/will your institution receive payment(s)?11	Add a second employer?	What is the name and role of the organization(s)?12	How does the interest relate to guideline topic?13	Is there a contractual agreement to disseminate product information?14	Did/will you receive payment(s)?15	Did/will your institution receive payment(s)?16	In the case that further employers are required, please use the open text entry below.
No												
No												
No												
No												
No												
No												
No												
No												

No						
Yes	Optum, general healthcare	Company prescribed medication for atopic dermatitis	No	No	No	No
Yes	Dr. Rachel Asiniwasis Medical Prof Corp.	I work in a very underserviced area in midwestern Canada. I have a very heavy medical dermatology practice and a large base of AD patients to care for, thus, it is my area of interest.	No	Paid as per routine specialist consultation/follow-up by local/provincial health region	Paid as per routine specialist consultation/follow-up by local/provincial health region	No
No						
No						
No						
No						
No						
No						
Yes	University of Colorado	I have no idea. All I know is that dermatology, a separate division from ours, does eczema studies. National Jewish, who is an affiliate of the University, does research in eczema. I am not involved in any of this, but it falls under "employer". Most if not all of us are at large universities where there may be many ongoing studies/activities related to eczema that do not involve any of us on the panel. We may not even be aware of such activity. I have to question the relevance of this.	No	No	Maybe? Have no idea. Not involved. Again, this is highly indirect and not relevant.	No
No						
No						

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Have you given, or are expecting to give relevant 'expert testimony' over the preceding 36 months and the next 12 months?	Expert testimony for which organization(s)?	What is the name and role of the organization(s)?17	How does the interest relate to guideline topic?18	Did/will you receive payment(s)?19	Did/will your institution receive payment(s)?20
No					
No					
No					
No					
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No					
No					
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No						
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No						
No						
No						

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Have you received, or are expecting to receive Grants over the preceding 36 months and the next 12 months?	Grants were received from which organization(s)?	What is the organization's role? If funding was for a study, please specify whether or not the organization had any role in: study design; data collection, access, analysis, or interpretation; writing of the report; or the decision to publish	How does the interest relate to guideline topic?21	Is there a contractual agreement to disseminate product information?22	Did/will you receive payment(s)?23	Did/will your institution receive payment(s)?24
Yes	Regeneron-Sanofi; Novartis, Allakos, Celgene,	Clinical trial site, involved in study design, data collection, analysis and writing report	Dupilumab is approved drug for AD	No	No	Yes
Yes	National Science Foundation, National Institutes of Health, Arizona Biomedical Research Centre	Grant awards have been made to both Arizona State University and Sequitur Health Corp. for research and development on a variety of topics: water purification membranes and medical device development.	My research and grant awards are not related to the guideline topic.	No	No	No
Yes	Pfizer, Inc	Produces pharmaceuticals for AD	Grant was for development of an educational handbook for managing and coping with AD. Handbook mentions treatments being reviewed in the handbook.	No	No	Yes
No						
Yes	Pfizer Kiniksa Nivartis Dermira	Pfizer: support basic science research proposal other clinical trials	investigated drugs in AD or other inflammatory condition	Yes	No	Yes
Yes	NIH, Sanofi Genzyme, Leo, Sacchi Foundation	They are all mechanistic studies on AD except for Leo, which is a topic treatment for AD	the guideline may mention some of these products and mechanisms of actions	No	No	Yes
Yes	AbbVie, National Eczema Association, Regeneron/Sanofi Genzyme, AOBiome	Investigator grants for research related to atopic dermatitis. Specifically dupilumab, upadacitinib, and Mother Dirt topical probiotic.	There are both directly and indirectly discussed in the guidelines.	No	Yes	No
Yes	N/A	Unknown, will likely participate in grant funded research in the next 12 months as a medical student	Most likely will not related to this topic	Unknown	Unknown	Unknown

Yes	NIH	NIH funding CoFAR studies on food allergy treatment and birth cohort	food allergy	No	No	Yes
No						
Yes	Leo	Organization funded an educational project valued around $8,000 for nursing and dermatologist-led educational project on AD management in remote and northern clinical stations in western Canada, primarily remote Indigenous communities (2022).	Educational project for AD (nursing and dermatologist led).	No	No	No payment was provided for myself, just for nursing educational support program.
Yes	1. Genentech USA, Inc 2. Pfizer	1. Funding for food allergy study. Company had no role in study design, data collection, analysis, interpretation, writing nor publishing decision. 2. Funding for atopic dermatitis handbook creation and study. Company had no role in study design, data collection, analysis, interpretation, writing nor publishing decision.	1. No relation 2. Guideline is about atopic dermatitis and handbook was developed for AD.	No	No	Yes
No						
No						
No						
No						
Yes	Galderma	Funding	outcomes research in atopic dermatitis	No	No	Yes
Yes	AHRQ	K08 award. They had no role in anything but funding the research.	No role	No	No	They received the grant
No						
No						

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Have you undertaken, or are expecting to undertake contractual research over the preceding 36 months and the next 12	Contractual research was undertaken with which organization(s)?	What is the organization's role?	How does the interest relate to guideline topic?25	Is there a contractual agreement to disseminate product information?26	Did/will you receive payment(s)?27	Did/will your institution receive payment(s)?28

mon ths?						
Yes	Sanofi-Regeneron, Novartis, Celgene	Involved in clinical trial, data collection	Dupilumab is approved drug for Atopic dermatitis	No	No	Yes
No						
No						
No						
No						
No						
Yes	AbbVie, Regeneron/Sanofi Genzyme, AOBiome	These companies make products for atopic dermatitis, dry skin, and itch. They were all directly involved in all aspects of the studies.	Guideline will mention commonly used drugs produced by this company and by others	No	Yes	No
No						
Yes	Aimmune, DBV Technologies, Regeneron	Pharmaceutical studies on food allergy treatment	food allergy	No	No	Yes
No						
Yes	Saskatchewan Health Authority	Academic funding for project entitled, "Virtual Dermatology Clinics in Remote and NOrthern Saskatchewan Indigenous Communities: Addressing Challenges and Exploring Opportunities."	Not related although we do see a high burden of AD in these remote Indigenous communities.	No	No	Yes
Yes	1. Regeneron 2. DBV Technologies	1. I was an investigator for the trial of dupilumab in adolescents. I was involved in data collection. I also was involved in the analysis of the laboratory studies obtained and assisted in writing the manuscript about this. I also am an investigator in the preschool study and was involved in writing an abstract about this study and will be involved in writing the manuscript. I am an investigator in a long term open label dupilumab study. 2. I have been an investigator for 4 completed studies of the Viaskin peanut patch. I was involved in data collection and writing the manuscripts. I am currently an investigator for 3 ongoing studies.	1. Guideline will mention dupilumab and will review these studies. 2. No relation	No	No	Yes
No						
Yes	1. Regeneron 2. Incyte	1. produces biologic for atopic dermatitis 2. produces topical JAK inhibitor for AD	Guideline discusses treatment of atopic dermatitis	No	No	Yes
No						
No						
No						
Yes	DBV, Aimmune, Novartis, Caprior, ARS	Food allergy and anaphylaxis research. They are the sponsor of phase 2/3 clinical trials our site and my team was involved in as a PI/co-I	unrelated	No	No	Yes
No						
No						

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Have you contributed to relevant educational events in the last 36 months, or are you expecting to do so in the next 12 months?	Lectures/educational events for which organization(s)?	What is the name and role of the organization(s)?29	How does the interest relate to guideline topic?30	Is there a contractual agreement to disseminate product information?31	Did/will you receive payment(s)?32	Did/will your institution receive payment(s)?33
Yes	Medscape, Uptodate	Educational veiw	Talks on Atopic dermatitis	No	Yes	No
No						
No						
No						
No						
Yes	Integrity Continuing Education	Revolutionizing AD, AAP	All lectures are related to AD	No	Yes	No
Yes	Pierre Fabre, Regeneron/Sanofi Genzyme, Pfizer, La Roche-Posay, Galderma, Eli Lilly, LEO Pharma, Incyte, MyOR Diagnostics, AbbVie	These companies produce products for AD and eczema and dry skin	Guideline will mention commonly used drugs produced by this company and by others	No	Yes	No
Yes	Student in all fist year medical school classes at Tufts University School of Medicine since 7/27/2021, will finish first year and continue to second year in the next 12 months.	Tufts University School of Medicine Medical School	Immunology, allergy, and dermatology topics will be covered.	No	No	Yes
Yes	AAAAI, ACAAI, AAP, NY Allergy Society, FL Allergy Society, KY Allergy Society	medical organizations	food allergy and anaphylaxis talks	No	Yes	No
No						
Yes	University of Saskatchewan, University of Alberta, University of Toronto	Academic institutions	I have been asked to present on various dermatology topics and on my experience working in remote and northern Indigenous communities.	No	No	Small honorarium for CME and resident lectures for some but not all.
Yes	Lectures on Atopic Dermatitis for Boston Children's Hospital, Massachusetts general hospital, Brigham and Women's Hospital, University of Wisconsin Madison Pediatric Grand Rounds	academic organizations	Guideline is on atopic dermatitis	No	Received honorarium for pediatric grand rounds and for Brigham CME course	No
Yes	American Academy of Family Physicians	AAFP is a national family medicine organizations that hosts didactics on a number of relevant family medicine topics	One of the AAFP Family Medicine Update Sessions was on Atopic Dermatitis	No	$600	No
Yes	AAAAI, ACAAI, regional, state and local societies, CME programs with grants from pharma (e.g. Regeneron Sanofi Genzyme)	Regeneron Sanofi Genzyme produce biologic therapy for atopic dermatitis	Guideline will review treatments of atopic dermatitis	No	Yes	No
No						
No						
Yes	American Academy of Dermatology, American College of Allergy Asthma and Immunology, European Academy of Dermatology and venereology, Revolutionizing Atopic Dermatitis, Maui Dermatology, Innovations in Dermatology	Conference	Atopic dermatitis lectures	No	Yes	No

Yes	Multiple State/local/national/international allergy societies and the AAP	Multiple State/local/national/international allergy societies and the AAP	unrelated	No	Yes	No
No						
No						

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Have you been engaged: to give presentations for a company which has a contractual right to control the content; and/or to act as the company's spokesperson in disseminating product information?	Presentations were given for which organization(s)?	What is the organization's role?34	How does the interest relate to guideline topic?35	Did/will you receive payment(s)?36	Did/will your institution receive payment(s)?37
No					
No					
No					
No					
No					
No					
Yes	Regeneron/Sanofi-Genzyme, Pfizer, AbbVie, Eli Lilly, Incyte, LEO Pharma	Produce products for AD and adjacent	Guideline will mention commonly used drugs produced by this company and by others	Yes	No
No					
No					
No					
Yes	Pfizer, Eli Lilly, Abbvie, Leo	Speakers bureau for biologic therapy relevant to AD and psoriasis. For AD - Tralokinumab, abrocitinib, upadacitinib, crisaborole.	Guideline will mention medications used by these companies (biologic/systemic/small molecules)	Yes	Yes
No					
Yes	American Academy of Family Physicians	National organization for family medicine	didactics given on atopic dermatitis	Yes	No
Yes	Regeneron Sanofi Genzyme	Produces biologic (dupilumab) for atopic dermatitis	Guideline will address treatments for atopic dermatitis	Not in past 2 years	No
No					

No					
Yes	Abbvie, Eli Lilly, Leo Pharma, Pfizer, Regeneron, Sanofi-Genzyme	Sponsor	Atopic Dermatitisa	Yes	No
No					
No					
No					

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Have you developed educational material for an organization apart from your employer in the last 36 months, or are you expecting to do so in the next 12months?	Educational material was developed for which organization(s)?	What is the organization's role?38	How does the interest relate to guideline topic?39	Is there a contractual agreement to disseminate product information?40	Did/will you receive payment(s)?41	Did/will your institution receive payment(s)?42
Yes	Uptodate	educational venue	Expert opinion on Atopic dermatitis	No	Yes	No
No						
No						
No						
No						
No						
Yes	LearnSkin and National Eczema Association	LearnSkin is an educational company for clinicians. The NEA is a patient advocacy group, non-profit	I'm not sure! I've never been asked this question before and am not sure how it could affect the guidelines.	No	No	No
No						
No						
No						
Yes	University of Saskatchewan	Academic institution	None relevant for AD except for one lecture to med students. This is standard teaching and educational material for our College of Medicine UGME.	No	No	Yes
No						
Yes	American Family Physician	journal for the American Academy of Family Physicians	journal article on the topic of atopic dermatitis was published in 2020	No	No	No

Yes	Lucid	Non branded educational material for multidisciplinary approach to atopic dermatitis	n/a	n/a	Yes	No	
No							
No							
No							
Yes	AAAAI, ACAAI, AAFA, Allergy and Asthma Network, IFPIES	professional allergy society or advocacy group	not related	No	Yes	No	
Yes	AAAAI	They are the a professional society	They are the guideline sponsor. The educational material was on food allergy (how to read food labels)	No	No	No	
No							

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Have you prepared or written manuscripts for an organization apart from your employer in the last 36 months, or are you expecting to do so in the next 12 mo	Manuscripts were prepared for which organization(s)?	What is the organization's role?43	How does the interest relate to guideline topic?44	Is there a contractual agreement to disseminate product information? 45	Did/will your institution receive payment(s)?46	Did/will your institution receive payment(s)?47

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No						
No						
No						
No						
No						
Yes	Atopic Dermatitis Research Network	NIH-sponsored project	Mechanistic studies on AD	No	No	Yes
No						
No						
No						
No						
Yes	AAAAI/ACAAAI	Assisted with clinician input and review on bleach baths in AD systematic review/meta analysis manuscript.	As above.	No	No	No
Yes	1. Regeneron with other 103. Siegfried EC, Bieber T, Simpson EL, Paller AS, Beck LA, Boguniewicz M, Schneider LC, Khokhar FA, Chen Z, Prescilla R, Mina-Osorio P, Bansal A. Effect of Dupilumab on Laboratory Parameters in Adolescents with Atopic Dermatitis: Results from a Randomized, Placebo-Controlled, Phase 3 Clinical Trial. Am J Clin Dermatol. 2021 Mar;22(2):243-255. Epub 2021 Mar 3. PMID: 33655423 2. DBV technologies . Fleischer DM, Shreffler WG, Campbell DE, Green TD, Anvari S, Assa'ad A, BÃ©gin P, Beyer K, Bird JA, Brown-Whitehorn T, Byrne A, Chan ES, Cheema A, Chinthrajah S, Chong HJ, Davis CM, Ford LS, Gagnon R, Greenhawt M, Hourihane JO, Jones SM, Kim EH, Lange L, Lanser BJ, Leonard S, Mahler V, Maronna A, Nowak-Wegrzyn A, Oriel RC, O'Sullivan M, Petroni D, Pongracic JA, Prescott SL, Schneider LC, Smith P, Staab D, Sussman G, Wood R, Yang WH, Lambert R, Peillon A, Bois T, Sampson HA. Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results. J Allergy Clin Immunol. 2020 Jul 10:S0091-6749(20)30957-X. doi: 10.1016/j.jaci.2020.06.028. Online ahead of print. PMID: 32659313 Fleischer DM, Greenhawt M, Sussman G, Schneider L, et al. Effect of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Ingestion Among Children With Peanut Allergy: The PEPITES Randomized Clinical Trial. JAMA. 2019 Feb 22. doi: 10.1001/jama.2019.1113. PMID: 30794314 Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, Cheema AS, Leonard SA, Pongracic JA, Sauvage-Delebarre C, Assa'ad AH, de Blay F, Bird JA, Tilles SA, Boralevi F, Bourrier T, HÃ©bert J, Green TD, Gerth van Wijk R, Knulst AC, Kanny G, Schneider LC, Kowalski ML, Dupont C. Effect of Varying Doses of Epicutaneous Immunotherapy vs Placebo on Reaction to Peanut Protein Exposure Among Patients With Peanut Sensitivity: A Randomized Clinical Trial. JAMA. 2017 Nov 14;318(18):1798-1809. PMID 29136445.	1. Manufacturer of Dupilumab 2. Manufacuturer of Viaksin peanut patch	1. Dupilumab will be reviewed in the guideline 2. No relation	No	No	No
Yes	American Family Physician	Journal for the American Academy of Family Physicians (AAFP)	wrote article on atopic dermatitis	No	No	No
Yes	AbbVie, LEO Pharma, Pfizer	Role of JAKs and JAK inhibition in AD, (not currently FDA approved) as well as role of biologic (tralokinumab in AD)	Guideline will discuss treatment of atopic dermatitis	No	No	No
No						
No						
No						

Yes	DBV					I have written up many study related manuscripts--it was their data from studies they sponsored	not related	No	No	No
No										
No										

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Have you planned, submitted or been awarded a patent over the preceding 36months and the next 12 months?	Patents were prepared for which product(s)?	What is the role of the product and the manufacturer?	How does the interest relate to guideline topic?48	Is this Patent licensed or unlicensed?	Did/will you receive payment(s)?49	Did/will your institution receive payment(s)?50
No						
Yes	point of care measurement devices	Point of care blood and urine measurement for liver and kidney diagnostics, the pending patent has been licensed to Sequitur Health Corp. from Mayo Clinic.	The pending patent does not relate to the guideline topic.	Licensed	I am a co-inventor of the patent, and in the future when Sequitur Health Corp. generates revenues I will receive payments from the patent.	In the future when Sequitur Health Corp. generates revenues the institutions (ASU and Mayo) will receive payment.
No						
No						
No						
No						
Yes	Theraplex AIM moisturizer	Topical anti-itch moisturizer for itch and eczema. Theraplex company.	Guideline will mention similar products	PENDING	Yes	No
No						
No						
No						
No						
No						

No					
No					
No					
No					
No					
No					
No					
No					

53

Have you received, or planning to receive equipment or supplies over the preceding 36 months and the next 12 months?	Equipment or supplies received from which organization(s)? *	What is the role of the organization(s)?	How does the interest relate to guideline topic?51	Did/will you receive payment(s)?52	Did/will your institution receive payment(s)?53
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					
No					

No					
No					

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Have you received, or planning to receive royalties over the preceding 36 months and the next 12 months?	Royalties were received from which organization(s)?	What is the name and role of the organization(s)?54	How does the interest relate to guideline topic?55	Did/will you receive payment(s)?56	Did/will your institution receive payment(s)?57
Yes	Uptodate	Educational	Expert opinion on AD	Yes	No
No					
No					
No					
No					
No					
Yes	Springer	Springer Company, textbooks	My textbook includes a chapter on atopic dermatitis	Yes	No
No					
Yes	UpToDate	medical information	food allergy topics	Yes	No
No					
No					
No					
No					
No					
No					
No					
No					
No					
Yes	McMaster	University	No relation	Yes	Yes

55

Have you received, or are planning to receive	Stock received from which organization(s)?	What is the organization's role?58	How does the interest relate to guideline topic?59	Did/will you receive payment(s)?60	Did/will your institution receive payment(s)?61

stock or payments from stock over the preceding 36 months and the next 12 months?					
No					
Yes	Have stock ownership in company I have co-founded, Sequitur Health Corp.	point of care diagnostics	This is not related to the guideline topic (atopic dermatitis)	No	No
No					
No					
No					
No					
Yes	STOCK OPTIONS: Altus Labs, Micreos, Concerto Biosciences, Boston Skin Science, YoBee Care	Some of these produce products in the AD space, others are working on products for AD or adjacent diseases	Guideline will mention some similar product categories.	No	No
No					
No					
No					
No					
Yes	Have stock options for Ukko	working on products for food allergy	No relation	No	No
No					
No					
No					
No					
No					
No					
No					
No					

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Have you received, or plan to receive expenses over the preceding	What was received, and from which organization(s)?	What is the organization's role?62	How does the interest relate to guideline topic?63	Is there a contractual agreement to disseminate product information?64	Did/will you receive payment(s)?65	Did/will your institution receive payment(s)?66

ng 36 months and the next 12 months ?										
No										
No										
No										
No										
No										
No										
Yes	Regeneron/Sanofi Genzyme, Pfizer, AbbVie, Eli Lilly, LEO Pharma, Incyte	All companies for whom I speak will provide travel.	Guideline will mention commonly used drugs produced by this company and by others			No	Yes		No	
No										
Yes	AAAAI, ACAAI	medical societies	food allergy			No	Yes		No	
No										
No										
No										
No										
No										
No										
No										
No										
Yes	Multiple state/local/national allergy societies, JTFPP	they sponsored educational meetings	unrelated			No	this is asking if my travel costs were reimbursed....		No	
No										
No										

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Do you have any ad	Personal Beliefs	Previously Published Opinions	Institutional Relationships	Career Advancement	Advocacy and Policy Positions	If yes, are you involved in formulating or voting for positions? Please detail.	If yes, could results from this article conflict with policies you have promoted or are	Treatments and Testing	Please describe the person(s) or organization(s) involved.	What is the person/organization's role?	How does the interest relate to guideline topic?67

dicationalrelationshipstodisclose?							obligated to follow? Please detail.				
No	Not applicable	Uptodate, previous JTF guidelines	no	Not applicable	Member of AAAAI, ACAAI, Deputy editor for Annals of Allergy Asthma and Immunology	no	no	not appliacable	no	no
Yes	No.	No.	No.	Strong support.	No.			I have an unpaid Research Affiliate appointment in the Division of Nephrology and Hypertension at Mayo Clinic. My husband, Dr. Leslie Thomas, is a nephrologist at Mayo Clinic	Mayo Clinic is a medical provider and research institution	I don't think it's applicable.
No	No	Np	No	Institution would be supportive of my work on this project	No		No	N/A	N/A	N/A
No	No	No	No	None	No		No	None	N/a	N/a
No	I believe in the methods used for analysis and data; no personal beliefs	mostly invited lectures on the topic of AD treatment, but not specific on the guidelines	no direct revenues or benefit from the article	Supportive	no		yes	none	n/a	n/a
No	No	No	No	none	No	No	Yes: I prescribe many of the topical treatments in this	none	none	none

								guidelines such as topical steroids, topical calcineurin inhibitors, dupilumab.			
No	Only that we need to take the best care of patients that we can and get the best information to clinicians.	I have over 200 publications... many of them are editorials. I don't know how to convey all this here, but I think that is why they wanted me on this committee in the first place.	No.	N/A. I am mid-career and not interested in promotion in my institution as I am primarily focused on my clinical practice.	Not really. The National Eczema Association is important to me and I'm an Board member but I don't work for them nor am I influenced by them.	N/A	N/A	Well yes! I'm a board certified dermatologist in clinical practice and focus on AD! That's why I'm here! I don't know how useful someone would be if they didn't know these treatments, tests, and patients intimately.	N/A	N/A	N/A
No	No	No	Tufts University School of Medicine may use these guidelines in the future.	Research publication may benefit me in the future as I apply to residency programs	No			No	Dr. Lynda Schneider, Jennifer LeBovidge, Boston Childrenâ€™s Hospital	medical providers	I received care related to the guideline topic from these medical providers at this institution
No	no	no	no	supportive	no			yes, I see children with atopic dermatitis in my practice	n/a	n/a	n/a
No	No	No	No	None	No	No		No	Na	Na	Na
No	It would be nice to acknowledge that limited literature we have currently in a Canadian context demonstrates that atopic dermatitis is a commonly unaddressed condition in remote Canadian Indigenous communities, which needs to be further explored. I personally have used bleach baths in these populations, whereas personal experience has demonstrated some benefit with good risk-benefit profile. I am happy to write up a reference-based section for EDI on this topic. I also have a personal interest in racial and ethnic disparities in AD.	"Atopic dermatitis and skin infections are a poorly documented crisis in Canada's Indigenous pediatric population: It's time to start the conversation." https://europepmc.org/article/med/34850439	N/A	I am probably the only North American dermatologist actively trying to increase awareness and education around North American Indigenous peoples and skin disease in context of well documented health disparities in determinants of health. So far colleagues have been very supportive and interested in my work by inviting me to present at grand rounds (MUN, University of Calgary, University of MB).	N/A	N/A	N/A	I frequently use EASI, IGA, DLQI scores. I use bleach baths for moderate to severe AD in select case, and always advocate for C&S swabs in case of secondary infection, especially in areas at risk for CA-MRSA (eg. remote Canadian Indigenous communities). However, these communities face many potential barriers.	Pfizer - Clinical Trials	I was a Principal Investigator in abrocitinib Phase III studies (B7451029, B7451019).	Clinical trial investigator in experimental agent for AD (abrocitinib; Phase III trials).
No	No	1. Schneider LC, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, Novak N. Atopic Dermatitis: A Practice Parameter Update 2012. J Allergy Clin Immunol. 2013;131:295-9. 2. Togias A, Cooper SF, Acebal M, Assa'ad A, Baker J, Beck LA, Block J, Byrd-Bredbenner C, Chan ES, Eichenfield LF, Fleischer DM, Fuchs GJ, Furuta GT, Greenhawt MJ, Gupta RS, Habich M, Jones SM, Keaton K, Muraro A, Plaut M, Rosenwasser LJ, Rotrosen D, Sampson HA, Schneider LC, Sicherer SH, Sidbury R, Spergel	no	no effect	no	no	no	Yes - I take care of atopic dermatitis patients and utilize treatments discussed in the guideline.	My husband Leonard Zon was a co-founder of Amagma Therapeutics. Both he and my daughter receive consulting fees. The company is developing antibodies to protease inhibitors	Husband was co founder	In future company may develop an atopic dermatitis drug

		J, Stukus DR, Venter C, Boyce JA. Addendum Guidelines for The Prevention Of Peanut Allergy In The United States: Report Of The National Institute Of Allergy And Infectious Diseases-Sponsored Expert Panel. J Allergy Clin Immunol. 2017 Jan; 139(1):29-44. PMID 28449793. 3. Siegfried EC, Jaworski JC, Eichenfield LF, Paller A, Hebert AA, Simpson EL, Altman E, Arena C, Blauvelt A, Block J, Boguniewicz M, Chen S, Cordoro K, Hanna D, Horii K, Hultsch T, Lee J, Leung DY, Lio P, Milner J, Omachi T, Schneider C, Schneider L, Sidbury R, Smith T, Sugarman J, Taha S, Tofte S, Tollefson M, Tom WL, West DP, Whitney L, Zane L. Developing drugs for treatment of atopic dermatitis in children (â‰¥3 months to <18 years of age): Draft guidance for industry. Pediatr Dermatol. 2018 Mar 30. doi: 10.1111/pde.13452. [Epub ahead of print] Review. PMID: 29600515 4. Silverberg NB, Pelletier JL, Jacob SE, Schneider LC. AAP Section on Dermatology, Section on Allergy and Immunology. Nickel Allergic Contact Dermatitis: Identification, Treatment, and Prevention. Pediatrics 2020;145(5):e20200628							and is looking at possible uses in atopic dermatitis.		
No	no	published review article on atopic dermatitis	no	strong support	no			yes, often prescribe atopic dermatitis medications	n/a	n/a	n/a
Yes	Need for updated guidelines based on critical review of data	Author on previous Practice Parameters for AD, AD Yardstick, Expert Opinion on Treatment of AD, multiple chapters and review articles, abstracts and presentations	no	n/a as I am too senior in my position (no further advancement)	no	n/a	n/a	n/a	n/a	n/a	n/a
No	No	No	No	My institution would be supportive.	No			Yes. I am a General Pediatrician and I treat patients with atopic dermatitis.	My husband, James Wynn	My husband has multiple NIH grants related to neonatal sepsis.	Not related
No	No	No	Not as far as I know.	I am an individual contractor whose main employment revolves very little around eczema/atopic dermatitis care. The companies I work for, as far as I know, do not rely on finances or reputation that will be even modestly impacted by this project.	No			I have, at different times in my career, recommended to patients treatments that may be addressed by this guideline; however, the majority of my recommendations will also include that they should be discussed with the patient's doctor(s). I have not, nor will not, be financially compensated for any recommendations or options mentioned to patients.	myself, Elaine Kim	In the future, I may wish to create a health/lifestyle/skin care blog.	As I suffer from atopic dermatitis, I may include opinions on products or comments based on the recommendations of the guidelines.
No	No	I have published over 500 peer-reviewed manuscripts, including review articles and a textbook	No	Dont think it would change much. I am already approved to be promoted to professor. I will receive no financial benefits	no	n/a	n/a	Only as part of standard of care clinical practive	None	none	none

No	I think the NIAID early introduction guidelines sucked. I wrote 90% of that paper and then voted against it. My opinions on this are internationally known.	I have >225 publications and multiple abstracts/publications	I'd be shocked if they even followed my publications to know I was part of it....	Strong	just the JTFPP who is authoring this guideline	we only vote on what topics to write about, and in the end if we agree with the summary statement	No. First eczema paper	I treat eczema. Generally use wet wraps, TCS. Haven't prescribed any biologics for it nor do I prescribe TCI's or support food allergy testing and restriction for eczema treatment.	none	none	none
No	No	No	No	Routine career advancement for junior faculty and publications being one criteria.	No	No	No, free reign given on developing recommendations and following the evidence to guide decision making.	Yes, commonly suggest, recommend or prescribe, without remuneration or reward based on the nature of such prescriptions, topical treatments, immunotherapy, bleach baths, and systemic treatments. I strive to follow an evidence based approach including shared decision making.	not applicable	not applicable	not applicable
No	No	No	No	No more promotion in terms of academic rank possible	No			No	N/A	N/A	N/A