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Title: Guidelines of care for the management and treatment of atopic dermatitis in adults with topical therapies

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Abstract

Background: New evidence has emerged since the 2014 guidelines that further informs the management of AD with topical therapies. These guidelines update the 2014 recommendations for management of atopic dermatitis (AD) with topical therapies.

Objective: To provide evidence-based recommendations related to management of AD in adults using topical treatments.

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

Results: The workgroup developed 11 recommendations on the management of AD in adults with topical therapies, including non-prescription agents and prescription topical corticosteroids (TCSs), calcineurin inhibitors (TCIs), Janus kinase (JAK) inhibitors, phosphodiesterase-4 inhibitors (PDE-4), antimicrobials, and antihistamines.

Limitations: The pragmatic decision to limit the literature review to English-language randomized trials may have excluded data published in other languages and relevant long-term follow-up data.

Conclusions: Strong recommendations are made for the use of moisturizers, TCIs, TCSs, and topical PDE-4 and JAK inhibitors. Conditional recommendations are made for the use of bathing and wet wrap therapy and against the use of topical antimicrobials, antiseptics, and antihistamines.

Abbreviations Used

AAD: American Academy of Dermatology

AD: Atopic dermatitis

CI: Confidence interval

EASI: Eczema area and severity index

FDA: Food and Drug Administration

IGA: Investigator's Global Assessment

JAK: Janus kinase

NRS: Numerical rating scale

PDE-4: Phosphodiesterase-4

RCT: Randomized controlled trial

RR: Risk ratio

SCORAD: SCORing Atopic Dermatitis

SD: Standard difference

TCI: Topical calcineurin inhibitor

TCS: Topical corticosteroids

US: United States

VAS: Visual analogue scale

WWT: Wet wrap therapy

Scope & Objectives

The objective of this guideline is to provide evidence-based recommendations for the management of adult atopic dermatitis (AD) using topical therapies available and approved for use in the United States (US). The treatment of other forms of dermatitis, such as irritant dermatitis and allergic contact dermatitis in those without AD, are outside the scope of this document. Specifically, this evidence review covers the use of non-prescription topical agents (eg, moisturizers, bathing practices, and wet wraps) and pharmacologic topical modalities, including corticosteroids, calcineurin inhibitors, Janus kinase (JAK) inhibitors, phosphodiesterase-4 (PDE-4) inhibitors, antimicrobials, and antihistamines. Recommendations herein serve to update previously published topical therapy recommendations.[1] Use of topical therapies to manage AD in pediatric patients will be covered in a forthcoming guideline. Until the publication of the pediatric guidance, refer to the pediatric therapy recommendations previously published.[1]

Methods

A multidisciplinary work group conducted a systematic review to determine the effectiveness and safety of topically applied agents, currently available and approved in the US, for management of AD in adults (**Table I**) and employed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach for assessing the certainty of evidence and formulating and grading clinical recommendations. Strength of recommendation and supporting evidence is expressed as shown in **Table II**.[2-4]

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

Table I. Clinical Questions and Scope

1. What are the efficacy and safety of nonpharmacologic topical treatments for AD?		
2. What are the efficacy and safety of pharmacologic topical treatments for AD?		
3. What are the relative efficacy and safety of individual topical agents for the treatment of AD?		
4. What are the efficacy and safety of combination topical therapies (concomitant use of more than one topical agent) in the treatment of AD?		
Outcomes of Interest		
Efficacy Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician	
	Prevention of flares	
Safety Outcomes	Serious adverse events	
	Withdrawal due to adverse events	
	Infection	
Patient-Reported Outcomes	Change in patient-reported symptoms	
	Change in quality of life	
	Change in itch severity	
Scope		
Characteristic	**Inclusion Criteria**	**Exclusion Criteria**
Population	Adults (≥ 18 years of age) with a clinical diagnosis of AD (including "eczema" or "atopic eczema")	Immunocompromised patients, contact dermatitis, seborrheic eczema, varicose eczema, discoid eczema
Intervention	Topical agents available and approved for use (for any indication) in the US	Treatments not available or approved for use (for any indication) in the US
Study Design	Published RCTs in which study participants are investigated (inter-individual, parallel-arm trials)	Unpublished research, observational studies, case series, case reports, modeling studies, narrative reviews

185 *AD*, Atopic dermatitis; RCT, randomized controlled trial; *US*, United States

186

187 **Table II.** Strength of Recommendation and Certainty of Evidence

Strength of Recommendation	Wording	Implication[2-4]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risk and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; recommendation applies to most patients in most circumstances.
Good Practice Statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[4]
Conditional recommendation *for* the use of an intervention	"We conditionally recommend…"	Benefits are closely balanced with risks and burden; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"We conditionally recommend against…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Certainty of Evidence	**Wording**	**Implication[2,3]**
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low certainty evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

Definition

Atopic dermatitis (AD, also known as atopic eczema) is a chronic, pruritic inflammatory skin disease that occurs most frequently in children, but also affects many adults. It follows a relapsing course. AD is often associated with a personal or family history of allergic rhinitis and asthma.

Although the diagnosis of AD is usually made clinically, alternative or concomitant causes of dermatitis, such as allergic contact dermatitis or irritant contact dermatitis should also be considered and evaluated via comprehensive history taking and physical exam. Other diagnostic tests such as biopsy or patch testing should performed if warranted.[5]

Introduction/Background

Despite advances in systemic therapy of AD, topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. Each class of treatment will be discussed individually, with particular attention to dosing and efficacy. They can be utilized individually or in combination with other topical, physical and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. While some treatments are well-established (eg topical corticosteroids), others are newer and based on recent scientific advancements (eg topical JAK inhibitors).

Table III. Recommendation for the management of atopic dermatitis in adults.

No.	Recommendation	Strength	Certainty of Evidence	Evidence
Non-prescription therapies				
1.1	For adults with AD, we recommend the use of moisturizers. *Remark: The use of a particular moisturizer or active ingredient in an emollient cannot be recommended based on the limited available evidence.*	Strong	Moderate	6-16
1.2	For adults with AD, we conditionally recommend bathing for treatment and maintenance. *Remark: A standard for the frequency or duration of bathing appropriate for those with AD cannot be suggested based on the limited available evidence.*	Conditional	Low	17-22
1.3	For adults with moderate-to-severe AD experiencing a flare, we conditionally recommend the use of wet dressings.	Conditional	Low	23-27
Topical calcineurin inhibitors				

2.1	For adults with AD, we recommend the use of tacrolimus 0.03% or 0.1%.	Strong	High	28-36
2.2	For adults with mild-to-moderate AD, we recommend the use of pimecrolimus 1% cream.	Strong	High	37-44
Topical corticosteroids				
3.1	For adults with AD, we recommend topical corticosteroids.	Strong	High	45-55
3.2	For adults with AD, we recommend intermittent use of medium potency topical corticosteroids as maintenance therapy (2 times/week) to reduce disease flares and relapse.	Strong	High	50,53,54
Topical antimicrobials/antiseptics and antihistamines				
4.1	We conditionally recommend against the use of topical antimicrobials for AD in adults.	Conditional	Low	56-59
4.2	We conditionally recommend against the use of topical antihistamines for AD in adults.	Conditional	Low	30
4.3	We conditionally recommend against the use of topical antiseptics for AD in adults. *Remark: For patients with moderate-to-severe AD and clinical signs of secondary bacterial infection, bleach baths or the use of topical sodium hypochlorite may be suggested to reduce disease severity.*	Conditional	Very Low	15,18-22,60,61
Topical PDE-4 inhibitors				
5.0	For adults with mild-to-moderate AD, we recommend the use of crisaborole.	Strong	High	62-66
Topical JAK inhibitors				
6.0	For adults with mild-to-moderate AD, we recommend the use of ruxolitinib cream.	Strong	Moderate	67-69

AD, Atopic dermatitis; *PDE-4*, Phosphodiesterase-4; *JAK*, Janus kinase

Non-prescription therapies

Moisturizers

Moisturizers were shown to reduce signs, symptoms, and inflammation in AD, to improve AD severity and to increase time between AD flares. Topical moisturizers target xerosis by minimizing transepidermal water loss and improving stratum corneum hydration and are integral to nearly all AD management plans. While they may be used as monotherapy in some mild cases, they are typically utilized as part of a comprehensive regimen with pharmacologic treatments.

An analysis of five moisturizer studies (totaling nearly 500 patients) showed a standard mean difference (SMD) reduction in AD severity as measured by the SCORing Atopic Dermatitis [SCORAD] tool and the Eczema Area and Severity Index [EASI]) of 0.51 (0.17-0.85) (**e-Table 1**).[8,9,11,15,70] Results varied, however; and Belloni et al. found a small but significant improvement in AD severity (mean EASI score decreased from 28.3 to 24.3, p = 0.024) with use of a moisturizer containing hyaluronic acid, telmesteine, *Vitis vinifera*, and glycyrrhetinic acid,[8] Breternitz et al. did not find an improvement in SCORAD between a glycerol-based emollient and placebo in 24 patients.[9] Analysis of three studies demonstrated patient assessment of disease severity improved in the experimental groups (79% vs 42.9%), though it did not reach significance (Risk Ratio [RR] 2.24, 0.89-5.64).[6,8,10]

Moisturizers may also help reduce itch. Nakai et al. found a significant difference in itch improvement (assessed via VAS scores) between their treatment (moisturizing cream containing lipopolysaccharide derived from *Pantoea agglomerans*) and vehicle groups at week 4 (p <0.01).[13] Itch improvement was demonstrated in other studies,[8] though Marini did not note a significant difference between their treatment group (ectoine-containing cream) and the control group (a nonsteroidal anti-inflammatory cream).[11]

Moisturizer use in AD also helps prevent flares. In a 12-week randomized blinded left-right comparison study of 26 AD patients in a maintenance treatment phase, applying a water-in-oil emollient containing licochalcone A, omega-6-fatty acids, ceramide 3 and glycerol on one side, versus vehicle on the other, significantly reduced the number of relapses observed in the active formulation compared with the vehicle arm.

Various types of moisturizers, including emollients, occlusive agents and humectants are commercially available, each with its own mechanism leading to improved skin hydration. Additionally, studies examining moisturizer use in AD vary on the type of moisturizer, study design, and outcomes assessed. Thus, the use of any particular moisturizer or active ingredient in an emollient cannot be recommended based on the limited available evidence.

The literature on AD treatment supports a strong recommendation for moisturizer use based on moderate certainty evidence (**Table III**). Moreover, moisturizers are generally safe, with rare serious adverse effects. Examination of seven studies found adverse events (i.e. mild and cutaneous) occurring in 34.3% of patients in the treatment arms vs 22.1% of patients in the control arms (RR 1.32, 1.01-1.74),[6,8,10,14,15] though withdrawal due to adverse events is uncommon.[6,8] Important considerations in moisturizer use include allergenic potential (many vehicles and interventions contained common contact allergens and innumerable ingredients), palatability, paucity of data in AD patients with skin of color, and cost.

Two points warrant further mention: 1) while moisturizing is generally superior to lack of moisturizing, the vehicle in emollient studies is often as effective as the vehicle plus active ingredient; 2) studies of emollients usually do not examine the use of moisturizers on actively dermatitic/inflamed skin.

Bathing

Data on bathing for adults with AD is minimal. Proksh et al. found magnesium chloride ("dead sea salt") may help reduce skin redness compared to tap water but patients did not have active dermatitis, thus limiting conclusions (**e-Table 2**).[17] Bleach baths may be most helpful in

infection prevention and bacterial colonization seen in AD but most studies are in children; one study of 10 adults with AD compared to 10 controls found bleach baths are well tolerated, safe and do not have a negative impact on stratum corneum hydration, transepidermal water loss or pH, though data were gathered from only one 10-minute exposure (**e-Table 3**).[21] Another study comparing 18 patients receiving bleach baths twice weekly to 18 patients receiving distilled water baths twice weekly for 8 weeks found patients in the treatment group had a significant within-group reduction in EASI score at one month and a significant improvement compared to placebo group at 2 months.[22]

Based on low certainty evidence, bathing for treatment and maintenance in patients with AD can be conditionally recommended (**Table III**). Moisturizers may be applied soon after bathing to improve skin hydration in patients with AD.[71] However, a standard for the frequency or duration of bathing, temperature of water, type of soap, and use of water softeners and other bathing accessories for those with AD cannot be suggested based on the limited available evidence.

Wet wrap therapy

Wet wrap therapy (WWT) is an effective option to control AD flares and mitigate recalcitrant disease. A topical agent (typically a low or mid potency topical corticosteroid [TCS]) is applied to the skin, followed by a moistened cotton suit, gauze or bandages (first layer), followed by a dry external (second) layer. The wrap can be used anywhere from 1 hour to 1 day at a time, for up to several weeks if needed (potentiated topical steroid absorption due to occlusion may limit duration of WWT).

In addition to providing a physical barrier against scratching, WWT exerts its effects via occlusion of the topical agent, resulting in greater penetration and reduced water loss/greater hydration.

Most data on WWT are from pediatric patients.[23,25-27] Based on available pediatric data, WWT with TCS (+ emollient in some studies) are superior to emollient-based wet dressings (**e-Tables 4-6**).[26,27] A left-right comparison study of 24 patients with acute AD treated with prednicarbate plus WWT on one limb and prednicarbate alone on another limb demonstrated a significant improvement in SCORAD in the WWT compared to the steroid-only side ($p < 0.011$).[24] Furthermore, no side effects and no withdrawal effects were observed in both groups during the study for 14 days afterwards.

Of note, WWT requires increased effort and time, as well as patient education to ensure correctness. The benefit of WWT in mild disease relative to the effort required is questionable. However, for patients with moderate to severe AD, the work group proposes a conditional recommendation based on low certainty evidence. Most data on WWT are from pediatric AD patients,[23,25] precluding firm statements on use in adults (**Table III**).

Variability in the vehicle used (ointment vs cream, steroid vs emollient), the addition of topical corticosteroids, and the type of wrap material (eg cotton, polyester, etc.) make interpreting data on WWT difficult. Given the paucity of data, suggestions on optimal parameters for WWT cannot be provided. Furthermore, data are mixed on the risk of secondary infection in WWT.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs) are a safe anti-inflammatory option for AD, particularly when there is concern for adverse events secondary to corticosteroid use. Six studies comparing pimecrolimus 1% cream to vehicle in adults with AD demonstrated a significant improvement in disease severity (assessed via the Atopic Dermatitis Severity Index, EASI, Investigator's Global Assessment [IGA], and Total Sign score) with follow up ranging from 1-6 weeks (**e-Table 7**).[37,39-41,43,44] Similarly, based on 4 studies, there was a decrease in itch from baseline with follow-up from 1-6 weeks.[37,40,41,43] In a study of 198 AD patients, Kaufmann et al. demonstrated a significant improvement in just seven days of treatment with pimecrolimus (53% vs 20% >1-point reduction in IGA scores, $p<0.001$).[40] The same study found 81% of pimecrolimus-treated patients versus 63% of vehicle-treated patients achieved a >1 point numerical rating scale (NRS) itch score reduction in 1 week ($p<0.001$). Evaluation of data from two other studies found pimecrolimus 0.1% was significantly associated with mild to no itch (NRS scores of 0 or 1) (RR 2.09, CI 1.58-2.75) in AD patients.[41,43]

Pimecrolimus may also decrease flares and TCS use (**e-Table 7**).[38,42] A trial of 265 patients receiving pimecrolimus 1% cream twice daily versus 257 patients receiving vehicle demonstrated treatment with pimecrolimus significantly increased the mean number of days without TCS use for a flare (138.7+53.2 vs 152.0+44.0 days, $p<0.001$).[38] Serious adverse events and withdrawal due to adverse events are rare with rates similar to placebo.[37,38] Taken together, the effects of pimecrolimus are modest, reproducible, and with minimal adverse events.

Tacrolimus 0.1% and 0.03% were shown to be superior to vehicle based on investigator assessments in adult AD in 4 randomized trials (**e-Table 8**).[29,32,33,36] 211 adult AD patients were randomized to tacrolimus 0.03%, 209 AD patients were randomized to tacrolimus 0.1%, and 212

AD patients were randomized to vehicle twice daily for 12 weeks - 58/211 (27.5%), 77/209 (36.8%), and 14/212 (6.6%), respectively, achieved improvement by Physician's Global Assessment ($p<0.001$ for both treatment groups compared to vehicle).[32] The same study demonstrated a significant improvement in pruritus in tacrolimus-treated patients versus placebo ($p<0.001$); other studies have found a similar improvement in itch reduction among adult AD patients receiving tacrolimus.[29,35]

Tacrolimus 0.1% and 0.03% ointment result in statistically significant flare prevention and disease control when used intermittently from 2-3 times per week in patients with stable disease followed for 40 to 52 weeks.[28,36] Serious adverse events, withdrawal due to adverse events, and infection were all comparable to placebo in studies.[31,33,34,36] The primary side effects of tacrolimus appear to be local in nature (i.e. burning).

Based on three randomized trials, tacrolimus 0.1% is significantly more efficacious than pimecrolimus 1% based on IGA assessment of "clear" or "almost clear" (43.6% in tacrolimus group vs 25.1% in pimecrolimus group, RR 1.74, 1.40-2.16) (**e-Table 9**).[72-74] Paller et al. demonstrated mean EASI score reduction of 54.1% in 210 AD patients applying tacrolimus 0.1% vs 34.9% in 203 patients applying pimecrolimus 1% ($p=0.0002$) for six weeks.[74] Both TCIs appear to be well-tolerated, though tacrolimus may cause more local irritation, at least initially.[72,74] Skin infection and withdrawal due to adverse effects do not appear to differ between the medications.[73,74] Though tacrolimus may be more effective clinically, it is commercially available as an ointment only, while pimecrolimus comes as a cream; patients who prefer a cream vehicle, have milder disease, or may be more sensitive to local reactions may be better

candidates for pimecrolimus. Given the small number of studies, a formal recommendation of preferred use of a particular TCI cannot be made.

Based on a review of studies of TCIs compared to vehicle, there is high certainty evidence to strongly recommend the use of tacrolimus 0.1% and 0.03% to treat AD patients (**Table III**). In AD patients with mild to moderate disease, there is high certainty evidence to strongly recommend pimecrolimus 1% cream. Of note, recommendations were based heavily on consideration of change in clinical signs, as there are limited data on pruritus and quality of life outcomes for adult AD patients.

The FDA's black box warning of an elevated risk of cancer with TCIs may worry some clinicians and patients. Several long-term safety studies were conducted for TCIs and there is evidence of a somewhat increased relative risk of lymphoma with TCI use but not other cancers.[75] Given the low absolute risk of lymphoma, cancer risk from TCIs is likely not clinically meaningful.[76-79]

Topical corticosteroids

Targeting a variety of immune cells and suppressing the release of proinflammatory cytokines, TCS are the most commonly utilized FDA-approved therapy in AD. TCS are commonly used as first-line treatment for mild to severe dermatitis in all skin regions.

TCS are grouped into 7 classes, based on potency (i.e. very high potency = class I and very low potency = class VII) (**Table IV**). When choosing a TCS potency, is important to consider the anatomical site (i.e. using lower potency agents on the face, neck, genitals, and body folds). While some dermatologists prefer high and very high potency steroids (at least initially) to

365 control active disease, others use the lowest potency agent needed for the situation and increase
366 potency if needed.

367 **Table IV.** Relative potencies of topical corticosteroids. Reprinted with permission from: Paller
368 and Mancini.[80] Copyright 2011 Elsevier. Includes representative examples and not all available
369 agents.

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

370 There are over 100 randomized controlled trials examining the efficacy of topical steroids in AD
371 – they are effective in acute AD, chronic AD, pruritus due to AD, active disease and prevention

of relapses (**e-Tables 10-14**).[81-85] There is overwhelming literature and high certainty evidence to support the use of TCS in the treatment of AD – thus the work group strongly recommends their use (**Table III**). Due to variability in dosing, potency and quantity of application, large studies are needed to help determine optimal treatment regimens.

Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient.[86-88] Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach (available data indicate fewer and increased time between relapses with this strategy).[53,89,90]

High potency and very high potency topical corticosteroids

High potency steroids are a useful option for treating severe disease and flares. A study of betamethasone dipropionate for 3 weeks demonstrated 94.1% of patients in the treatment group showed either a good or excellent clinical response (vs. 12.5% of patients in the control group); additionally, an 86% improvement in the severity score was observed (vs. a 24.9% improvement in the severity score for the control group).[48] A 26-patient crossover study by Wahlgren et al. demonstrated that 4 days of betamethasone dipropionate cream reduced visual analogue scale (VAS) itch score in AD patients (days 3-4, $p<0.0001$; nights 3-4, $p<0.005$).[49] Side effects were minimal in both studies.

Very high potency TCS (i.e. clobetasol propionate, fluocinonide, halobetasol propionate) can be an effective option for controlling flares, particularly in severe AD. Three randomized trials demonstrated a change in severity over two weeks to clear/almost clear (67.2% vs 22.3% for

vehicle, RR 2.76).[45-47] Adverse events appear to be low (RR 0.13, 0.01-1.55, based on therapy discontinuation) over two weeks, with more withdrawals in the vehicle group than the treatment group.

Medium potency topical steroids and maintenance therapy

Though very high potency steroids may be prescribed for short courses due to the risk of atrophy, medium potency steroids can be utilized for longer courses due to a more favorable adverse event profile. Eichenfield et al. demonstrated fluticasone propionate 0.05% lotion daily for 4 weeks results in ≥50% lesion clearance plus stable/improved scores from baseline in ≥75% of 20 sign/symptom assessments (70.6% vs 28.6%, RR 1.86).[52] Dolle et al. found similar efficacy with fluticasone propionate 0.05% cream – at 22 days, the treatment group displayed a significant reduction in Three Item Severity score (sum of 3 intensity items: erythema, edema/papulation, excoriation) compared to the vehicle group.[51] Hydrocortisone butyrate 0.1% cream, a lower medium potency TCS, displayed a significant mean difference in total lesion score (7 disease signs evaluated on a 4-point scale) compared to placebo (mean difference 2.99 lower, 4.26–1.72 lower).[55]

Furthermore, three studies have demonstrated the use of fluticasone propionate 0.05% cream twice weekly results in significant reduction in relapse/flare.[50,53,54] In these studies, low rates of adverse events were observed. In a study by Hanifin et al, 117 adult AD patients were randomized to maintenance therapy with daily emollients and either intermittent fluticasone propionate 0.05% cream or vehicle once daily 4 days per week for 4 weeks, followed by once daily 2 days per week for 16 weeks. After achieving treatment success with up to four weeks of fluticasone propionate 0.05% twice daily, those treated with fluticasone propionate were 7.0

times less likely to have an AD relapse (95% CI: 3.0-16.7, p<0.001).[53] Based on high certainty evidence, we strongly recommend intermittent use of medium potency TCS as maintenance therapy (twice a week) to reduce disease flares and relapse.

Combination therapy

An eight-week randomized control trial examining the use of hydrocortisone butyrate ointment with mupirocin ointment did not demonstrate a benefit with combination therapy;[91] another four-week crossover study of clobetasol butyrate and mupirocin demonstrated similar results (**e-Table 15**).[92] Moreover, treatment with gentamicin with betamethasone valerate cream vs betamethasone valerate cream alone did not reveal any significant difference in change of overall severity scores from baseline between the two groups (**e-Table 16**).[93]

Conversely, Torok et al. found subjects receiving tacrolimus 0.1% ointment twice daily and clocortolone pivalate 0.1% cream twice daily achieved significantly better dermatologic sum scores (measure excoriation, induration and erythema) than patients receiving monotherapy with either tacrolimus 0.1% or clocortolone pivalate 0.1% (**e-Table 17**).[94]

Comparison to topical calcineurin inhibitors

Though comparative data are limited, high (i.e. betamethasone dipropionate 0.05%) and very high (clobetasol 0.05%) potency steroids appear to be more effective than pimecrolimus 1% cream (**e-Tables 18-19**).[39] The comparative data with medium potency steroids is less clear – while they do appear to be more effective than pimecrolimus in terms of change in severity and itch reduction, not all studies reached significance (**e-Table 20**).[41,95-97] There does not seem to be a difference in infection risk between pimecrolimus and medium potency TCS.[95]

Just as tacrolimus 0.1% ointment appears to be more effective than pimecrolimus 1% cream, it may be more effective when compared to medium potency topical steroids. In a study of over 500 AD moderate to severe AD patients, 264/283 (93.3%) of patients receiving tacrolimus vs. 245/279 (87.8%) fluticasone 0.005% ointment achieved ≥60% reduction in modified local eczema and severity index score (RR 1.03, 95%CI 0.91-1.17) (**e-Table 21**).[98] Similar results were reported in comparative studies between tacrolimus and class I-III TCS, hydrocortisone butyrate 0.1%, and hydrocortisone acetate 1%; skin infections, withdrawal due to adverse events, and serious adverse events do not appear to be different between groups (**e-Tables 22-23**).[99-102]

Adverse effects and monitoring

The incidence of adverse events with TCS is low.[103,104] Though TCS are associated with a variety of cutaneous side effects (i.e. purpura, telangiectasia, hypopigmentation, focal hypertrichosis, acneiform eruptions, and striae), skin atrophy is generally the most concerning for physicians and patients. Risk factors for atrophy include higher potency TCS use, occlusion, use on thinner and intertriginous skin, older patient age, and long-term continuous use. Allergic contact dermatitis to TCS or other ingredients in their formulations can be determined via patch testing.[105] The related concepts of Topical Steroid Addiction (TSA) and Topical Steroid Withdrawal (TSW) (see **Box 1**) are less clearly characterized in the literature. Two systematic reviews, the most recent in 2021, have analyzed published series and case reports and deemed the strength of the evidence low to very low.[106,107] The most consistent risk factors identified for TSA/TSW is prolonged, inappropriate use of potent topical steroids on the face or in intertriginous areas, which would be inadvisable in any case.

Box 1. Topical Steroid Addiction/Withdrawal Definition[106,107]

1. A cutaneous eruption that followed TCS use which either appeared: a) after discontinuation of TCS or b) when elevated doses and applications of TCS were needed to prevent it from appearing
2. The eruption was primarily localized to the site(s) of application
3. Resolution of the eruption at some point after TCS cessation was considered contributory to the diagnosis

Non-cutaneous side effects with TCS are rare but can occur. An association with cataracts or glaucoma is unclear, but minimizing periocular TCS use is advised.[103] Hypothalamic-pituitary-adrenal axis suppression can also occur with prolonged, continuous use of high potency TCS on large surface areas, particularly in those receiving corticosteroids in other forms (inhaled, intranasal, oral).[108] This can be assessed via a cortisol stimulation test.

Topical antimicrobials/antiseptics and antihistamines

Antimicrobials are sometimes necessary to treat infected lesions of AD (e.g., cellulitis, impetigo). In this guideline, we assessed the evidence and made recommendations regarding the use of antimicrobials to treat AD itself.

Various antimicrobials were studied in AD, but sample sizes were small and treatment durations were short (**e-Table 24**). Studies of endolysin, ciclopiroxolamine, sertraconazole, and hypericum did not demonstrate a significant improvement from baseline in disease severity (i.e. SCORAD and EASI) compared to placebo.[56-59] Sertraconazole 2% cream twice daily did not show a significant improvement in chronic pruritus in patients with AD in a double-blind, vehicle-controlled clinical trial of 70 patients.[59]

Considering antiseptics, two studies were analyzed for triclosan, both of which had adult patients (in addition to pediatric patients) (**e-Table 25**). Compared to a vehicle emollient, Tan et al. found a triclosan 1% emollient resulted in a significantly reduced mean change in SCORAD from baseline at day 14 but not day 27; of note, all subjects were able to use betamethasone valerate 0.025% cream, though the experimental group used a significantly lower amount.[15] A similar study of 50 patients by Breneman et al. found a significant improvement in severity and extent of skin lesions in the group receiving triclocarban 1.5% soap vs. the placebo soap group over a six week study period; subjects were allowed to use triamcinolone acetonide 0.025% cream, and there was no difference in utilization between groups.[60]

Although utilization of antimicrobials and antiseptics carries a risk of antimicrobial resistance, alteration of microflora and pH, and potential contact sensitization, there was no difference in the rate of serious adverse events between the treatment and placebo groups in the aforementioned antimicrobial studies of endolysin and hypericum,[56,58] and no withdrawals in the study of triclosan 1% emollient.[15]

Our systematic review only identified one study of a topical antihistamine to treat AD. Topical doxepin, used in 132 patients for 1 week, led to a reduction of 68.6% vs 54.6% in the control group in pruritus VAS scores ($p<0.01$) (**e-Table 26**). Withdrawal due to adverse events was higher in the experimental group (12.1% vs 2.2%; RR 5.08, 95% CI 1.51-17.06). Patients may experience drowsiness, which occurs due to systemic absorption, and allergic contact dermatitis. Of note, diphenhydramine 2% gel is available over the counter, but no studies met the inclusion criteria for these guidelines.

The work group conditionally recommends against the use of topical antimicrobials, topical antihistamines, and topical antiseptics for AD based on low certainty evidence (**Table III**).

Topical phosphodiesterase-4 inhibitor

A topical PDE-4 inhibitor (crisaborole 2%) was approved for use in AD by the US Food and Drug Administration (FDA) in 2016. It is indicated in mild to moderate disease and used as an alternative to TCS and TCIs.

Four randomized trials comparing topical PDE-4 inhibitor therapy to vehicle in adult AD were included for analysis (**e-Table 27**). PDE-4 inhibitor use led to a small but significant improvement in dermatitis in all 4 studies.[62,64-66] Across two identical trials, 1,016 AD patients (aged 2-79) were randomized to crisaborole 2% ointment twice daily and 506 to vehicle for 28 days.[66] On day 29, significantly more crisaborole-treated patients achieved Investigator's Static Global Assessment success (clear or almost clear with 2-grade or greater improvement from baseline): 326 (32.1%) vs 110 (21.7%) ($p<0.0001$; RR 1.80, 95%CI 1.48-2.18).

Crisaborole has also demonstrated efficacy in the pruritus of AD in three studies.[62,64,66] In 40 adults with AD, two AD lesions of identical severity were randomized to crisaborole ointment 2% or vehicle twice daily or 14 days.[62] The mean change from baseline in lesion itch NRS at day 15 was greater for crisaborole-treated than vehicle-treated lesions (-3.9 vs -2.0, $p<0.0001$).

Topical PDE-4 inhibitors appear to have a favorable safety profile (i.e. small percentage of patients with application burning, stinging, and/or pain) and discontinuation rate comparable to placebo (**e-Table 27**).[63,66] The work group strongly recommends its use for mild to moderate AD, based on high certainty evidence.

Topical JAK inhibitors

Topical JAK inhibitors are a relatively new topical treatment in AD. Topical ruxolitinib 1.5% cream was approved for short-term and non-continuous chronic treatment of mild-moderate AD in patients 12 years of age and older by the FDA in 2021. The treatment area should not exceed 20% body surface area, and a maximum of 60 grams should be applied per week; these stipulations are aimed at reducing systemic absorpation, as black box warnings include serious infections, mortality, malignancies (e.g. lymphoma), major adverse cardiovascular events, and thrombosis.

Two randomized trials demonstrated efficacy for adult AD with 277/531 (52.2%) ruxolitinib-treated patients achieving an IGA score of 0-1 or an improvement of ≥2 points compared to 33/296 (11.1%) of vehicle-treated patients (**e-Table 28**).[109,110] Similarly, two randomized trials found benefit in itch reduction in adult AD – 270/519 (52.0%) vs 43/279 (15.4%) of the experimental and placebo groups, respectively, achieved ≥4 point reduction in itch NRS scores over 8 weeks (RR = 3.38, 2.54-4.51) (**e-Table 28**).[110,111]

The mean percent improvement from baseline in Skindex-16 overall scores (a measure of health-related quality of life) in patients treated with ruxolitinib 1.5% cream twice daily was 63.5% at week 2 (vehicle = 10.5%, p=0.001) and 73.2% at week 8 (vehicle = 19.7%, p<0.001).[111] Serious and emergent adverse events are rare and occurred at similar rates to vehicle. Application site burning, pain and pruritus may occur at a rate similar to or even lower than vehicle.[109,110]

Based on moderate certainty evidence, there are enough data to strongly recommend topical JAK inhibitors in AD. However, this recommendation is based on the currently available short-term

efficacy and safety data and may require updating in the future as long-term safety data become available.

Gaps in Research

There are significant gaps in our current understanding of various topical AD therapies. Directing future research towards these gaps will improve patient safety and satisfaction. Overall, studies are needed which examining patient outcomes and quality of life data, as well as long term follow up, and use in special and diverse populations (e.g. pregnancy, lactation, immunosuppression, multiple comorbidities, skin of color, pediatric).

Studies of moisturizer use in AD vary widely in methods, duration, endpoints and active ingredients, making it difficult to draw conclusions and compare or aggregate data from various studies. Future studies should prioritize standardization of study methods and study endpoints, larger sample sizes, and sufficient follow up times. Additionally, studies examining variations in bathing, along with additives such as sodium hypochlorite and magnesium chloride, would be a welcome addition to the literature. Similarly, further research is called for to augment WWT data in adults, as well as optimal technique – currently, there is variability in topical therapy (e.g. use of TCS, optimal vehicle, use of emollient), use of antiseptic solution in the wraps, composition of wrap material (e.g. cotton, polyester, etc.).

Two decades of experience with TCIs in AD have answered many questions regarding safety and chronic use. Continuing to collect data on patients who have used these treatments for many years will bolster confidence among providers and their patients particularly in those using the

medication chronically. Furthermore, the use of TCIs in a scheduled manner for flare prevention warrants further exploration

Despite their use as first line therapy and longevity in AD treatment, many questions remain about TCS. Gaps requiring further research include comparative data (i.e. between different TCS and topical AD treatments with different mechanisms), cost effectiveness data, long-term data, safety data (particularly for high and very high potency TCS), and use for flare prevention.

Finally, for the newer topical AD treatments – PDE4 inhibitors and JAK inhibitors – long-term safety and efficacy data are welcome. Efficacy and safety compared to more established treatments like TCIs and TCSs could help guide providers as they manage difficult cases. Furthermore, concerns about the use of topical JAK inhibitors, particularly due to systemic absorption, need clarification; long term data will better elucidate if any of the concerning side effects seen in systemic JAK inhibitors can also occur with the topical formulation.

Work Group Members' Disclosures

The information below represents the authors' disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk*. In accordance with AAD policy, a minimum 51% of Work Group members did not have any relevant conflicts of interest.

Participation in one or more of the listed activities below constitutes a relevant conflict:

- service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved.
- sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on atopic dermatitis or atopic dermatitis drugs in development or FDA-approved

If a potential conflict was noted, the work group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group

consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

Ali Alikhan, MD, has no relationships to disclose. Lionel Bercovitch, MD, has no relationships to disclose. David E. Cohen*, MD, MPH, serves on the board of directors for Timber and Evommune receiving stock options and/or fees; as a consultant for Asana Biosciences, Ferndale Laboratories, Inc., Novartis, Facilitation of International Dermatology Education, Dermavant Sciences, Leo Pharma, Inc., UCB, and Cosmetic Ingredient Review receiving honoraria and/or stock options. Dawn M.R. Davis, MD, has no relationships to disclose. Lawrence F. Eichenfield*, MD, serves on the board of directors for Forte Biosciences and Verrica Pharmaceuticals, Inc., receiving honoraria and/or stock options; as an investigator for Abbvie, Arcutis, Dermavant, Galderma Laboratories, Pfizer and Bausch, receiving research grants, fees and/or honoraria; as a consultant for Abbvie, Almirall, Arcutis, Asana, Dermavant, Eli Lilly, , Galderma, Ichnos/Glenmark, Incyte, Janssen, Leo Pharma, Novartis, Ortho Dermatologics, Otsuka, Pfizer, Regeneron, and Sanofi Genzyme, honoraria; as an independent contractor for Elsevier, Inc. receiving royalties. Lindsy Frazer-Green, PhD, has no relationships to disclose. Jennifer Moyer Darr, LCSW, has no relationships to disclose. Amy S. Paller*, MD, serves as a consultant for Abbvie, Abeona, Almirall, Amagma, Anaptysbio, Arena, Bausch, Bristol Myer Squibb, Dermavant, Dermira, Eli Lilly, Exicure, Forte, Leo, Lifemax, Novartis, Phoenix, Pierre Fabre, Pfizer, Rapt, Regeneron, Sanofi, Sol-Gel, UCB, and Venthera receiving honoraria; as an investigator for Anaptysbio, Eli Lilly, Incyte, Janssen, Krystal Bio, Lenus, Regeneron, and UCB receiving no compensation. Kathryn Schwarzenberger, MD is the founder of Pretel, Inc. and serves as a data safety monitoring board member for Pfizer, Inc. receiving fees. Robert Sidbury*, MD serves as an advisory board member for Pfizer, Inc. receiving honoraria; as a principal investigator for Regeneron receiving grants and research funding; as an investigator for Brickell Biotech, Inc., and Galderma USA receiving grants and research funding; as a consultant for Galderma Global and Microes receiving fees or no compensation. Jonathan I. Silverberg*, MD, PhD, MPH, serves as an advisory board member for BioMX, Boehringer Ingelheim, RAPT Therapeutics, Celgene, Ortho Dermatologics, TARGET Pharma, AFYX Therapeutics, Corrona, Inc., Dermira, Pfizer, Inc., Leo Pharma, Inc., and Menlo Therapeutics receiving honoraria and/or fees; as an investigator for DS Pharma, TARGET Pharma, Kiniksa Pharmaceuticals, Ltd., Menlo Therapeutics, GlaxoSmithKline, AbbVie, Leo Pharma, Inc., and Regeneron receiving research funding, honoraria, or no compensation; as a consultant for AOBiome, Bluefin Biomedicine, Bodewell, BiomX, Inc., Galderma Research & Development, LLC., Arena Pharmaceuticals, Dermavant Sciences, Incyte Corporation, DS Biopharma, Sun Pharmaceutical Industries, Ltd., AnaptysBio, Asana Biosciences, LLC., Pfizer, Inc., Glenmark Generics, Inc., Sanofi, Kiniksa Pharmaceuticals, Ltd., GlaxoSmithKlein, Eli Lilly and Company, AbbVie, Regeneron, and Medimmune receiving honoraria or fees; as a speaker for the Fall Clinical Dermatology Conference, Maui Derm, and Regeneron receiving honoraria or fees. Anne Marie Singh, MD, as a consultant for Abbvie. Peggy Wu, MD serves as an author for UpToDate, Inc receiving honoraria.

Appendix 1 Detailed Methods

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (D.D. and R.S.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on and voting for recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 10 members, an additional member serving as a methodologist, and a representative from a patient advocacy organization. The Work Group was supported by an AAD guidelines staff member with health research methodology expertise.

Formulation of Questions and Rating the Importance of Outcomes

Based on the aim of the systematic review to determine how effective and safe currently available and approved topical agents are for the management of AD in adults, the expert Work Group identified four clinical questions, using the Population, Intervention, Comparator, Outcome (PICO) format (**Table I**). Next, the Work Group identified outcomes considered important for making clinical decisions regarding the topical treatment of AD through discussion and review of the core outcome set for AD trials developed by the Harmonizing Outcome Measures for Eczema (HOME) initiative (**Table 1**).[112] The Work Group ranked the importance of each primary outcome for decision-making via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).[113] Results of voting were used to categorize outcomes as "critical", "important", or "not important".

Table 1. Primary Outcomes

Primary Outcome	**Importance Ranking**
Change in clinical signs/symptoms of disease as assessed by clinician	Critical
Prevention of flares	Critical
Serious adverse events	Critical
Withdrawal due to adverse events	Critical
Infection	Important
Change in patent-reported symptoms	Critical
Change in quality of life	Critical
Change in itch severity	Critical

Literature Searches

AAD partnered with the Southern California Evidence Review Center (SCERC) at the University of Southern California to conduct components of the systematic review process, including literature searches, study selection, risk of bias assessment, data extraction, and analysis. The Southern California Evidence Review Center performed a search of the literature for all PICO questions using MEDLINE (via PubMed), EMBASE, and clinicaltrials.gov to identify reports of randomized controlled trials (RCTs). In addition, MEDLINE, the Cochrane Database of Systematic Reviews, and PROSPERO were queried to identify systematic reviews for reference-mining. Databases were searched without publication year restriction. However, the evidence base supporting the current recommendations was restricted to publications from November 1, 2012, through May 21, 2020 to identify RCTs published since completion of the search that informed the topical therapy recommendations in the AAD's 2014 guidelines of care for the management of AD. For treatments not addressed in the 2014 guidelines, results from searches conducted from inception to May 2020 were included. Additionally, the publications cited in the 2014 guidelines in support of topical therapy recommendations were reviewed and those meeting the inclusion criteria for the current review were included in the evidence base regardless of publication date. This approach served to update the review conducted in support of the previous iteration of the AD guidelines while allowing for transition to new development methodologies. The searches identified 2,161 citations. A large proportion of citations was identified through the previous guideline and other published systematic reviews.

Study Selection

Studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection by the SCERC. Two reviewers independently screened citations. All citations deemed relevant by one or both reviewers were obtained as full text. Two independent reviewers screened full text citations against the *a priori* established eligibility criteria (**Table 2**); discrepancies were resolved through discussion. Of the 2,161 search results, 1,127 were obtained as full text and 368 RCTs reported in 430 publications that met inclusion criteria. Of the selected studies, only those including adults with a clinical diagnosis of AD were included in the present evidence base. Studies including pediatric populations will inform additional recommendations in a forthcoming pediatric focused guideline.

Table 2. Eligibility Criteria for Topical Management of Adults with AD

Category	**Criteria**
Population	Adults (≥ 18yo) with clinically diagnosed AD
Intervention	Nonpharmacologic and pharmacologic topical agents available and approved for use in the US. Including one of the following or a combination of: moisturizers, prescription emollient devices, bathing practices, oils, wet wraps; topical immunosuppressive agents; topical corticosteroids; topical calcineurin inhibitors; topical PDE-4 inhibitors; aryl hydrocarbon receptor activators; topical JAK inhibitors; topical antimicrobials and antiseptics; topical antihistamines; other topical treatments
Comparator	Placebo-controlled; head-to-head trials; multi-arm trials
Outcomes	Change in clinical signs/symptoms of disease as assessed by clinician; Prevention of flares; Serious adverse events; Withdrawal due to adverse events

	Infection; Change in patent-reported symptoms; Change in quality of life; Change in itch severity
Study Design	Published RCTs, including parallel, cross-over, and cluster RCTs, randomizing different clusters, patients, or body sites for individual participants
Other	English language studies

Data Extraction

The SCERC used structured data abstraction forms designed in online software for systematic reviews. Data extraction was initially performed by an independent reviewer with subsequent quality control performed by a second reviewer.

Risk of Bias Assessment and Evidence Synthesis

Risk of bias was assessed in all included studies by the SCERC using critical appraisal domains compatible with Cochrane Collaboration's tool for assessing risk of bias in randomized trials (ROB2).[114]

Following risk of bias assessment, the Cochrane Collaboration Review Manager, version 5.3 was used to conduct meta-analyses when data were homogenous and poolable. Individual estimates were pooled using a random-effects model and the method of DerSimonian and Laird.[115,116] For dichotomous and continuous outcomes risk ratios and mean differences with accompanying 95% CIs were reported, respectively. Statistical heterogeneity was assessed using the Higgins I^2 value and the χ^2 test. A Higgins' I^2 value ≥ 50% and P values < .05 were considered to represent significant heterogeneity. Subgroup analyses were planned *a priori* for short-term (≤ 16 weeks) and long-term (> 16 weeks) outcomes.

Narrative synthesis was conducted when meta-analysis was not possible due to insufficient data reporting, differences in study designs, interventions, or comparators, or statistical heterogeneity suggesting that an average effect across studies is not useful.

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence for each critical or important outcome.[117] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall certainty of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**Table 3**).

Table 3. Certainty of Evidence Ratings

Certainty of the Evidence	Confidence in the Estimate of Effect
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Formulating and Grading Recommendations

The Work Group drafted recommendations using the evidence profiles and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, and feasibility.[2] In accordance with the GRADE approach, recommendations were either "strong" or "conditional".[3] The implications of each strength of recommendation are summarized in **Table 4**. Recommendations were also graded according to the GRADE approach.[3] In situations in which the supporting evidence for a recommendation was indirect only, but the certainty surrounding an intervention's impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed.[4] Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

Table 4. Strength of Recommendation Implications

Strength	**Implication**
Strong	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh the benefits
Conditional	Benefits finely balanced with risks and burden

Manuscript Review and Currency Statement

This guideline was developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.[118] This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

746

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