Acad Med J 2025;5(Suppl 1):S27-S35.
UDC: 616.5-056.3-097
https://www.doi.org/10.53582/AMJ255127n
Guidelines

GUIDELINES FOR TOPICAL TREATMENT OF PATIENTS WITH ATOPIC DERMATITIS AT THE UNIVERSITY CLINIC FOR DERMATOLOGY IN SKOPJE

Najdova Anita, Popovski Tomche, Adjievska Nevenka, Jakovljevic Natasha, Risteska Kristina, Viranova Gordana, Ristevska Sofija, Damevska Katerina

University Clinic for Dermatology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia
e-mail: anitanajdova@yahoo.com

Abstract

This Guideline was developed for the needs of the PHI University Clinic for Dermatology, Skopje, and is based on the European Guidelines for Local Therapy of Atopic Dermatitis (AD) from December 2020 and July 2021 (EuroGuiDerm Guideline). The process involved specialist physicians from the University Hospital for Dermatology with extensive experience in pediatric dermatology and the treatment of patients with atopic dermatitis (AD), as well as resident physicians involved in the technical preparation of the text. The Professional Board of the University Clinic for Dermatology in Skopje adopted the Guideline in February 2025. The first part of the Guideline contains general information about the goals and scope, the health issues covered in the Guideline, the target groups, and a methodology section. The Guideline provides guidelines for identifying patients who should be treated with topical therapy, recommendations, and information for each drug and emollient. This Guideline includes recommendations and information on essential therapy with emollients and moisturizers, topical anti-inflammatory, antimicrobial, and antipruritic treatment, UV phototherapy, techniques for avoiding provocative factors, and recommendations for nutrition, complementary medicine, and education for patients with AD.

Objectives of the guidelines

This Guideline aims to provide guidelines for the topical treatment of patients with AD of varying severity for all age groups. It includes new and already established topical therapies for AD, updated according to the latest available evidence.

The target population is patients with AD of all age groups. The primary health questions regarding AD are the following:

- What is the optimal topical treatment appropriate to the needs of patients, taking into account efficacy, safety, and the presence of comorbidities?
- How to best manage and monitor the selected therapy?

The recommendations are evidence-based, considering the results of systematic reviews obtained with rigorous methods and the practical experience of experts.

Target group of users of the guidelines

The Guideline is primarily intended for dermatologists at the University Hospital for Dermatology in Skopje.

Methodology

These guidelines are based on EuroGuiDerm, the Method Manual version 1.3. , available on the EDF website: https://www.guidelines.edf.one/guidelines/atopic-ezcema [[1]]

Guideline development and consensus process

The chapters and recommendations were developed by a working group of specialist physicians at the Dermatology Clinic with extensive experience in pediatric dermatology and the treatment of patients with AD, as well as resident physicians involved in the technical preparation of the text.

Each chapter and all recommendations were reviewed, discussed, and amended where necessary. The Expert Collegium and then the Management Board of the University Clinic for Dermatology in Skopje, reviewed and adopted the Guideline with the necessary consensus.

Evidence

The systematic review by Drucker et al.[2] was used as the evidence base for the decision-making framework. The certainty of the evidence compared to placebo[3] is added for each evidence-based recommendation.

Emollient therapy

Basic emollient therapy is the cornerstone of any treatment for AD.[1,2] Emollients contain a humectant or moisturizer (encourages hydration of the stratum corneum) such as urea or glycerol and an occlusive (reduces evaporation). Emollients are “medicated medium” topical formulations without active ingredients, while emollient pluses are those with additional active, non-medicinal substances[3].

A Cochrane review compared emollient-containing emollients with those without a moisturizer and found that the former were more effective in reducing the severity of AD and reduced the use of corticosteroids (CS)[4].

Some studies have examined oil-based emollients compared to non-medicated treatment or "medication medium" and found no significant differences between the groups. In one study, the oil group had fewer exacerbations and reduced the use of topical CS. Overall, the combined use of emollients was more effective than emollient-only treatments in various outcomes[4,5].

We recommend applying emollients immediately after bathing or showering and gently patting dry. A small study suggests that emollients applied alone without bathing may have a more prolonged effect[6]. Only preparations without protein allergens or haptens that cause contact allergies (lanolin or preservatives such as methylisothiazolinone) should be used, especially in children under 2 years of age[7].

Long-term maintenance therapy with emollients (e.g., twice weekly) after remission may prolong flare-free periods. Skin hydration is usually maintained by daily application of emollients with a hydrophilic base containing, for example, 5% urea or glycerol [8].

Table 2. General recommendations for topical medications for the treatment of AD[1]

Overall recommendations	TCS↑↑		TCI↑↑	
	TCS class I and II	TCS class III and IV	Tacrolimus 0.1% Tacrolimus 0.03%	Pimecrolimus 1%
For further information, see the background text	class I is not suitable for long-term proactive treatment; Long-term proactive treatment only class II	acute flare; Proactive treatment with TCS class III class IV is not for long-term daily treatment or head and neck; class IV is not recommended for proactive treatment either	acute flare; Long-term proactive treatment; especially in the face, intertriginous sites, anogenital area	acute flare; especially in the face, intertriginous sites, anogenital area
Most important side effects	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis	skin atrophy telangiectasia striae distensae ecchymosis hypertrichosis perioral dermatitis corticosteroid addiction syndrome Suppression of adrenal function	initial warmth, tingling, or burning	initial warmth, tingling, or burning
	TCI class II and III are off-label for proactive treatment		In the label for proactive treatment	not suitable for proactive treatment
Special considerations				
Suitable for **children > 2 to <16** years of age	yes	yes	yes (0.03%) [2]	yes[2]
Suitable for **babies** < 2 years of age	yes	under special supervision	yes (0.03%) [1]	yes (from the age of 3 months)[2]
Suitable during **pregnancy**	yes	yes	yes (0.03% & 0.1%)[1]	yes[1]
Suitable during **breastfeeding**	yes	yes	yes (0.03% & 0.1%)[1]	yes[1]
Suitable for pruritus	yes	yes	yes (0.03% & 0.1%)	yes

[1] off label use; [2] licensed use;

The galenic aspects of the formulation should be considered with seasonal differences (higher hydrophilicity in summer, higher lipid content in winter) and according to the affected region (pastes for intertriginous areas, not too oily for the face).

It is recommended that barrier ointments, bath oils, shower gels, emulsions, or micellar solutions that improve the barrier effect be used.

The amount of topical medication applied is crucial; approximately 250g per week is recommended.[3] The fingertip unit rule can be followed; this is sufficient to apply to two palms of an adult, which is approximately 2% of the body surface area of an adult [9]. The cost of quality emollients often limits their use, as such therapies are over-the-counter in Macedonia.

Using pure oils, such as coconut or olive oil, instead of emulsions will dry out the skin and increase transepidermal water loss, so they are not recommended.

Emollients with non-medicinal active ingredients (emollient pluses)

Some non-medicinal topical treatment products contain potentially active ingredients.These products, called "emollient pluses" according to the 2018 European guideline, may contain flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plant extracts[10], bacterial lysates from Aquaphilus dolomite or Vitreoscilla filiformis species [11,12], or synthetic menthol derivatives such as menthoxypropanediol[3].

Various ingredients, such as urea, glycerol, or propylene glycol, enhance the emollient's moisturizing effect. Emollients may also be enriched with other ingredients (hydrating agents or tannin, ammonium bitumen sulfonate, flavonoids, or unsaturated fatty acids, such as omega-3/omega-6 compounds).

Role of emollients in prevention

Emollients have a clear role in secondary and tertiary prevention in patients with AD. There is conflicting evidence for the primary preventive effects of emollients: infants at high risk for AD who were treated daily with emollients developed less AD in the first year of life[13].

Care and bathing

Skin hygiene procedures play an important role in the treatment of AD, especially in infants and young children. Some authors consider alkaline soaps unfavorable compared to liquid cleansers with appropriate skin pH and lipid content[14]. The water temperature should not be high [15]. The skin should be cleansed gently and carefully to remove crusts and mechanically eliminate bacteria. Cleansers are available in different galenic forms (syntheses, aqueous solutions) and should not contain strong allergens[9]. pH values should be between 5 and 6. Adding antiseptics, such as sodium hypochlorite (bleach bath), is beneficial.

Anti-inflammatory treatment

Currently, approved topical anti-inflammatory therapies include corticosteroids (TCAs), calcineurin inhibitors (CNIs), and a phosphodiesterase 4 (PDE-4) inhibitor, which is approved in the European Union but not yet available on the market.

The amount of topical anti-inflammatory agents should follow the fingertip unit rule. Topical medications should be applied to hydrated skin, mainly when ointments are used. Topical anti-inflammatory therapy can be implemented in two approaches: reactive and proactive. Within the framework of reactive treatment, anti-inflammatory agents are applied only to the skin with lesions and are discontinued or rapidly reduced when the lesions improve. Proactive therapy is usually applied twice weekly to previously affected skin areas, in combination with daily use of emollients, with a pre-established clinical review schedule[16].

Proactive treatment begins after acute treatment when lesions have been successfully treated with regular anti-inflammatory therapy [17].

Patients with acute erosive lesions sometimes do not tolerate standard topical therapy and may be treated first with "moist dressings." Moist dressings are very effective in acute AD and improve the tolerance of emollients. Moist dressings with diluted or lower potency CS (group II, III, typical dilutions are 1:3–1:10. Usually, only a few days of application are sufficient) [18]. However, this treatment approach is not yet standard.

Topical corticosteroids

Topical corticosteroids (TCS) are the first-line anti-inflammatory treatment, usually applied to acutely inflamed skin according to the patient's needs (itching, sleep disturbance, new episodes) [19].

According to Niedner, the potency of TCS is grouped from mild/low (class I) to superpotent (class IV)[20]. The choice of TCS should consider the galenic formulation, the patient's age, and the area to which the drug will be applied. In children, TCS with low to moderate potency should be used routinely. Adolescents and adult patients can use potent to very potent TCS under specialist supervision in acute AD flares for a short period. Potent and very potent TCS are sometimes used in younger age groups under specialist supervision.

Treatment of the facial region and especially the periorbital region or other sensitive areas (wrinkles and neck) should be limited to mild to moderate TCAs (class I and II) [21].
With mild disease activity, a small amount of TCA is applied twice to three times a week (monthly amounts in the average range of 15 g in infants, 30 g in children, and up to 60–90 g in adolescents and adults, adjusted for surface area), associated with liberal use of daily emollients provides good maintenance treatment. Monitoring by clinical examination for cutaneous side effects with long-term use of potent TCAs is critical.

Topical calcineurin inhibitors (TCIs)

Two TCIs (tacrolimus ointment and pimecrolimus cream) are licensed to treat AD. Pimecrolimus cream 1% and tacrolimus ointment 0.03% are approved in the EU for 2 years of age and above. Elidel cream is additionally approved in Europe from 3 months of age. Tacrolimus ointment 0.1% is licensed only for patients aged 16 years and older. TCIs are first-line therapy for sensitive areas where the use of TCIs is associated with adverse effects. In children, twice-weekly treatment with tacrolimus 0.03% ointment has been reported to reduce the number and intervals between exacerbations [22].

None of the TCIs induce skin atrophy and are associated with an increased risk of non-melanoma skin cancer, other malignancies, or photocarcinogenesis. These findings favor their use in sensitive areas of the body (eyelids, perioral, genital, axillary, or inguinal) and make them suitable for long-term use [23].

Monitoring for cutaneous adverse effects is important during long-term treatment with TCIs.

Local phosphodiesterase-4 inhibitors

The local phosphodiesterase 4 (PDE-4) inhibitor crisaborole is approved for the treatment of mild to moderate AD in patients aged 2 years and older in the United States, Canada, Australia, Israel, and Hong Kong. The European Union approved crisaborole in 2020, but it has not been commercialized in the European market. Therefore, no recommendations are made.

New local therapies

New local therapies include several local Janus Kinase (JAK) inhibitors[24].

Ruxolitinib

In a 4-week study, the selective JAK 1 and JAK 2 inhibitor ruxolitinib showed similar or greater efficacy in mild to moderate AE compared with triamcinolone cream (a class III TCS) and was recently approved in the United States [25].

Other JAK inhibitors with similar or different selectivity (brepocitinib) are developing for local therapy, but none are currently licensed in Europe.

Antimicrobial treatment

The prevalence of Staphylococcus aureus (SA) colonization in patients with AD is over 80% at the lesion site and 40% on nonlesional skin, compared with 10% in healthy individuals[26]. Bacterial swabs are usually useless, as they do not alter the treatment approach unless the patient is infected with a resistant bacterial strain.

Viral infections, including herpes simplex, varicella zoster, molluscum contagiosum, measles, and coxsackie viruses, occur more frequently in patients with AD, with a tendency for disseminated, widespread disease [27].

Vaccination

Regional vaccination programs should screen all patients with AD as recommended.

Antipruritic treatment

Topical calcineurin inhibitors significantly relieve itching in AD [28].

The systemic anti-inflammatory agent dupilumab has a high efficacy in reducing itching [29]. Similar data exist for tralokinumab, abrocitinib, baricitinib, and upadacitinib.

UV phototherapy alleviates itching in AD, as demonstrated in several studies [30]. A Cochrane review found no evidence that H1 antihistamine (HA) treatments are effective as an "add-on" therapy for AD, compared to placebo [31]. In particular, first-generation systemic HAs may affect sleep quality and reduce REM sleep. Therefore, regular long-term use of sedating antihistamines is not recommended[32].

Phototherapy and photochemotherapy

Photo(chemo)therapy can be used in patients with moderate-to-severe AD that does not respond to topical therapy. Current knowledge about the safety of phototherapy in patients with AD is poor because there are no registries with long-term follow-up[33].

Dietary interventions

Food allergy has been documented in approximately one-third of children with moderate to severe AD [34]. Among food allergens, cow's milk, hen's eggs, peanuts, soy, tree nuts, and fish are most commonly responsible for immediate-type food allergy and exacerbation of AD in young children[35].

A recent Cochrane review identified 39 randomized controlled trials involving 2599 randomized participants[36]. The authors concluded that currently available probiotic strains make little or no difference in improving eczema symptoms compared with no probiotic use. A systematic review of dietary supplements, including fish oil, vitamin D, or vitamin E, concluded that there is no convincing evidence for the benefits of dietary supplements in AD[37].

Conflict of interest statement. None declared.

References:

1. Wollenberg A, Kinberger M, Arents B, Aszodi N, Avila Valle G, Barbarot S, et al. European Guideline (EuroGuiDerm) on atopic eczema – part II: non-systemic treatments and treatment recommendations for special AE patient populations. *J Eur Acad Dermatol Venereol*. 2022;36:1904–26. doi:10.1111/jdv.18429
2. Drucker AM, Lam M, Prieto-Merino D, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Living Systematic Review and Network Meta-Analysis Update. *JAMA Dermatol*. 2024 Sep 1;160(9):936-944. doi: 10.1001/jamadermatol.2024.2192. Erratum in: *JAMA Dermatol*. 2024 Sep 1;160(9):1012. doi: 10.1001/jamadermatol.2024.3600.
3. Drucker AM, Ellis AG, Bohdanowicz M, et al. Systemic immunomodulatory treatments for patients with atopic dermatitis: a systematic review and network meta-analysis. *JAMA Dermatol*. 2020;156(6):659–67. doi:10.1001/jamadermatol.2020.0729
4. Van Zuuren EJ, Fedorowicz Z, Christensen R, Lavrijsen A, Arents BWM. Emollients and moisturisers for eczema. *Cochrane Database Syst Rev*. 2017;2:CD012119. doi:10.1002/14651858.CD012119.pub2
5. Akerstrom U, Reitamo S, Langeland T, et al. Comparison of moisturizing creams for preventing atopic dermatitis relapse: a randomized double-blind controlled multicentre clinical trial. *Acta Derm Venereol*. 2015;95(5):587–92. doi:10.2340/00015555-1996
6. Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. *Pediatr Dermatol*. 2009;26(3):273–8. doi:10.1111/j.1525-1470.2009.00890.x
7. Dinkloh A, Worm M, Geier J, Schnuch A, Wollenberg A. Contact sensitization in patients with suspected cosmetic intolerance: results of the IVDK 2006-2011. *J Eur Acad Dermatol Venereol*. 2015;29(6):1071–81. doi:10.1111/jdv.12692
8. Wollenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. *Immunol Allergy Clin North Am*. 2010;30(2):351–68. doi:10.1016/j.iac.2010.02.002
9. Gelmetti C, Wollenberg A. Atopic dermatitis– all you can do from the outside. *Br J Dermatol*. 2014;170(Suppl 1):19–24. doi:10.1111/bjd.13034
10. Mengeaud V, Phulpin C, Bacquey A, Boralevi F, Schmitt AM, Taieb A. An innovative oat-based sterile emollient cream in the maintenance therapy of childhood atopic dermatitis. *Pediatr Dermatol*. 2015;32(2):208–15. doi:10.1111/pde.12541
11. Gueniche A, Knaudt B, Schuck E, et al. Effects of nonpathogenic gram-negative bacterium Vitreoscilla filiformis lysate on atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled clinical study. *Br J Dermatol*. 2008;159(6):1357–63. doi:10.1111/j.1365-2133.2008.08927.x
12. Aries MF, Hernandez-Pigeon H, Vaissiere C, et al. Anti-inflammatory and immunomodulatory effects of Aquaphilus dolomiae extract on in vitro models. *Clin Cosmet Investig Dermatol*. 2016;9:421–34. doi:10.2147/CCID.S111277
13. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818–23. doi:10.1016/j.jaci.2014.05.043
14. Uehara M, Takada K. Use of soap in managing atopic dermatitis. *Clin Exp Dermatol*. 1985;10(5):419–25. doi:10.1111/j.1365-2230.1985.tb00557.x
15. Denda M, Sokabe T, Fukumi-Tominaga T, Tominaga M. Effects of skin surface temperature on epidermal permeability barrier homeostasis. *J Invest Dermatol*. 2007;127(3):654–9. doi:10.1038/sj.jid.5700626

16. Wollenberg A, Frank R, Kroth J, et al. Proactive therapy of atopic eczema – an evidence-based concept with a behavioral background. *J Dtsch Dermatol Ges*. 2009;7(2):117–21. doi:10.1111/j.1610-0387.2008.07197.x
17. Wollenberg A, Ehmann LM. Long-term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol*. 2012;24(3):253–60. doi:10.5021/ad.2012.24.3.253
18. Gonzalez-Lopez G, Ceballos-Rodriguez RM, Gonzalez-Lopez JJ, Feito Rodriguez M, Herranz-Pinto P. Efficacy and safety of wet wrap therapy for patients with atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2016;177(3):688–95. doi:10.1111/bjd.14604
19. Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol*. 2002;147(3):528–37. doi:10.1046/j.1365-2133.2002.04964.x
20. Niedner R. Therapie mit systemischen Glukokortikoiden. *Hautarzt*. 2001;52(11):1062–71.
21. Barnes L, Kaya G, Rollason V. Topical corticosteroid-induced skin atrophy: a comprehensive review. *Drug Saf*. 2015;38(6):493–509. doi:10.1007/s40264-015-0275-6
22. Reitamo S, Van Leent EJ, Ho V, et al. Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol*. 2002;109(3):539–46. doi:10.1067/mai.2002.121375
23. Queille-Roussel C, Paul C, Duteil L, et al. The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol*. 2001;144(3):507–13. doi:10.1046/j.1365-2133.2001.04128.x
24. Bissonnette R, Papp KA, Poulin Y, et al. Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial. *Br J Dermatol*. 2016;175(5):902–11. doi:10.1111/bjd.14606
25. Kim BS, Howell MD, Sun K, Papp K, Nasir A, Kuligowski ME. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145(2):572–82. doi:10.1016/j.jaci.2019.07.034
26. Totte JE, van der Feltz WT, Hennekam M, van Belkum A, van Zuuren EJ, Pasmans SG. Prevalence and odds of Staphylococcus aureus carriage in atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol*. 2016;175(4):687–95. doi:10.1111/bjd.14633
27. Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum: a retrospective analysis of 100 cases. *J Am Acad Dermatol*. 2003;49(2):198–205. doi:10.1067/mjd.2003.93
28. Sher LG, Chang J, Patel IB, Balkrishnan R, Fleischer AB Jr. Relieving the pruritus of atopic dermatitis: a meta-analysis. *Acta Derm Venereol*. 2012;92(5):455–61. doi:10.2340/00015555-1400
29. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of Dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335–48. doi:10.1056/NEJMoa1610020
30. Garritsen FM, Brouwer MW, Limpens J, Spuls PI. Photo(chemo)therapy in managing atopic dermatitis: an updated systematic review with implications for practice and research. *Br J Dermatol*. 2014;170(3):501–13. doi:10.1111/bjd.12669
31. Matterne U, Böhmer MM, Weisshaar E, Jupiter A, Carter B, Apfelbacher CJ. Oral H1 antihistamines as 'add-on' therapy to topical treatment for eczema. *Cochrane Database Syst Rev*. 2019;1:CD012167. doi:10.1002/14651858.CD012167.pub2

32. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)- antihistamines: a GA(2)LEN position paper. *Allergy*. 2010;65(4):459–66. doi:10.1111/j.1398-9995.2009.02257.x
33. Vermeulen FM, Gerbens LAA, Schmitt J, et al. The European TREatment of ATopic eczema (TREAT) registry taskforce survey: prescribing practices in Europe for phototherapy and systemic therapy in adult patients with moderate-to-severe atopic eczema. *Br J Dermatol*. 2020;183(6):1073–82. doi:10.1111/bjd.18700
34. Tsakok T, Marrs T, Mohsin M, et al. Does atopic dermatitis cause food allergy? A systematic review. *J Allergy Clin Immunol*. 2016;137(4):1071–8. doi:10.1016/j.jaci.2015.09.033
35. Sicherer SH, Sampson HA. Food hypersensitivity and atopic dermatitis: pathophysiology, epidemiology, diagnosis, and management. *J Allergy Clin Immunol*. 1999;104(6 Pt 1):S114–22. doi:10.1016/s0091-6749(99)70077-8
36. Makrgeorgou A, Leonardi-Bee J, Bath-Hextall FJ, et al. Probiotics for treating eczema. *Cochrane Database Syst Rev*. 2018;11:CD006135. doi:10.1002/14651858.CD006135.pub4
37. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev*. 2012;2:CD005205. doi:10.1002/14651858.CD005205.pub3