Received: 11 January 2021 | Accepted: 31 March 2021

DOI: 10.1111/1346-8138.15921

THE JOURNAL OF DERMATOLOGY

ORIGINAL ARTICLE

Practical algorithm to inform clinical decision-making in the topical treatment of atopic dermatitis

Thomas Luger[1] | Uladzimir Adaskevich[2] | Maryna Anfilova[3] | Xia Dou[4] | Nikolay N. Murashkin[5,6,7] | Leyla Namazova-Baranova[7,8] | Oleg Nitochko[9] | Ashraf Reda[10] | Tetyana V. Svyatenko[11] | Zeynep Tamay[12] | Mohammad Tawara[13] | Elena A. Vishneva[7,8] | Svitlana Vozianova[14] | Hua Wang[15] | Zuotao Zhao[16]

[1]Department of Dermatology, University of Münster, Münster, Germany

[2]Vitebsk State Medical University, Vitebsk, Belarus

[3]National Pirogov Memorial Medical University, Vinnytsya, Ukraine

[4]Peking University Shenzhen Hospital, Shenzhen, China

[5]Medical Research Center for Children's Health, Federal State Autonomous Institution of the Ministry of Health of the Russian Federation, Moscow, Russia

[6]I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

[7]Paediatric and Child Health Research Institute of the Central Clinical Hospital of the Russian Academy of Sciences, Ministry of Science and Higher Education, Moscow, Russia

[8]Russian National Research Medical University, Moscow, Russia

[9]Odessa National Medical University, Odessa, Ukraine

[10]Mediclinic Welcare Hospital, Dubai, United Arab Emirates

[11]Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine

[12]Division of Pediatric Allergy and Clinical Immunology, Department of Pediatrics, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey

[13]Ishtar Center for Dermatology, Aesthetics and Laser Surgery, Eye Specialty Hospital, Amman, Jordan

[14]P.L. Shupyk National Medical Academy of Postgraduate Education, Kiev, Ukraine

[15]Children's Hospital of Chongqing Medical University, Chongqing, China

[16]Department of Dermatology and Venereology, Peking University First Hospital, Beijing Key Laboratory of Molecular Diagnosis on Dermatoses, National Clinical Research Center for Skin and Immune Diseases, Beijing, China

Correspondence
Thomas Luger, Dermatology Clinic, University of Münster, Von-Esmarch-Straße 58, Münster 48149, Germany.
Email: luger@uni-muenster.de

Funding information
Meda Pharma S.p.A., *a Viatris company*

Abstract

Atopic dermatitis is a chronic relapsing, inflammatory skin disorder associated with skin barrier dysfunction, the prevalence of which has increased dramatically in developing countries. In this article, we propose a treatment algorithm for patients with mild-to-moderate and severe atopic dermatitis flares in daily clinical practice. An international panel of 15 dermatology and allergy experts from eight countries was formed to develop a practical algorithm for the treatment of patients with atopic dermatitis, with a particular focus on topical therapies. In cases of mild-to-moderate atopic dermatitis involving sensitive skin areas, the topical calcineurin inhibitor pimecrolimus should be applied twice daily at the first signs of atopic dermatitis. For other body locations, patients should apply a topical calcineurin inhibitor, either pimecrolimus or tacrolimus, twice daily at the first signs of atopic dermatitis, such as pruritus, or twice weekly in previously affected skin areas. Emollients should be used regularly. Patients experiencing acute atopic dermatitis

flares in sensitive skin areas should apply a topical corticosteroid twice daily or alternate once-daily topical corticosteroid/topical calcineurin inhibitor until symptoms improve. Following improvement, topical corticosteroid therapy should be discontinued and patients switched to a topical calcineurin inhibitor. Maintenance therapy should include the use of pimecrolimus once daily for sensitive areas and tacrolimus for other body locations. This treatment algorithm can help guide clinical decision-making in the treatment of atopic dermatitis.

KEYWORDS
algorithm, atopic dermatitis, pimecrolimus, tacrolimus, therapeutics

1 | INTRODUCTION

Atopic dermatitis (AD) is a common chronic disease characterized by general skin dryness, eczematous lesions, and pruritus.[1] The worldwide prevalence of AD is estimated at 15–20% in children (aged 6–14 years) and 1–3% in adults;[2] however, there is substantial variation between countries,[3] and increases in the prevalence of AD have been observed over the past decade in developing countries.[4]

In China, the prevalence of AD in children has increased from 3% in 2004[5] to 13% in 2016,[6] although variations between urban and rural areas have been observed.[5] In Turkey, the prevalence of AD in children was 5% in 1994, 10% in 2004, and 7% in 2014,[7] and data published from Ukraine in 2018 reported that the prevalence of AD in children aged between 8 and 9 years in the Poltava region was 5%.[8] In 2010, a 10% prevalence of AD was observed in children from rural and urban areas of Belarus.[9] In Russia, data published between 2006 and 2016 reported that the incidence of AD was 6.2–15.5%, and was region dependent.[10,11] In 2016, 72% of all patients with AD were children (0–17 years old); 41% of these cases were among children aged 0–4 years.[11] The prevalence of AD among children aged 15–17 years was 1.16%.[10,11] In a study of allergic diseases conducted in Russian adolescents, the prevalence of AD was shown to be up to 5-times greater than that reported in official statistics.[12]

Alongside regional differences in the prevalence of AD, the progress and symptoms of AD can differ between races. Recent studies involving Asian, European American, and African American children and adults with AD have shown that AD is a complex disease characterized by different phenotypes related to age, chronicity of the disease, race, epidermal barrier, immunological status, and molecular endotypes.[13,14]

Events that happen during the first 1000 days of life, including those that occur during gestation, may increase an individual's predisposition to developing AD.[15] The microbiome of the intestine and skin have been found to play an important role in AD; dysbiosis of both the gut and skin microbiome have recently been linked to alterations in immune responses, and can result in skin diseases, such as AD.[16,17] Frequent use of antimicrobials, as well as early use of antibiotics, has been associated with changes in the gut microbiome, which has also been associated with AD.[18–22] Infants with *Staphylococcus epidermidis* or *Staphylococcus hominis* colonization experience milder AD than those colonized by *Staphylococcus aureus*.[17,23] Furthermore, studies investigating *S. aureus* colonization have shown that certain strains of *S. hominis* can prevent *S. aureus* colonization on the skin of patients with AD.[17] The increasing prevalence of AD in some developing countries may be attributed to lifestyle changes, including a Western diet.[24] Furthermore, food allergy is an increasingly common precursor to AD,[25,26] and is predisposed by food avoidance during infancy and childhood.[27,28]

Atopic dermatitis negatively impacts quality of life of patients and caregivers[29,30] and can predispose to mental health disorders,[31–34] highlighting that the prevention of AD progression must be considered through early and effective treatment. Proactive maintenance treatment, where therapies are applied in the absence of visible lesions, may also be required. Early diagnosis of AD is necessary for timely implementation of treatment and to prevent comorbid diseases by reducing contact with pro-inflammatory agents;[35,36] late diagnosis and subsequent undertreatment can lead to significant complications and further increases the burden of AD.[37] The general strategies adopted for treating AD should be adapted based on the patient's location, as geographical and genetic differences can lead to varying prevalence, presentation of symptoms, and availability of health care.[38]

In this article we propose a treatment algorithm for the management of patients with mild-to-moderate AD and severe flares in daily clinical practice, with a particular focus on topical treatments.

2 | METHODS

An international panel of 15 dermatology and allergy experts from eight countries (Belarus, China, Germany, Jordan, Russia, Turkey, Ukraine, and the United Arab Emirates) met to develop a practical algorithm for the treatment of patients with AD. The algorithm was developed based on a review of published treatment guidelines on AD, the experts' clinical experience, and an evaluation of relevant literature published up to May 2018.[39–46] The treatment algorithm has

been adapted for use in the Middle East[47] and in Asia[48] by separate groups of experts from these regions.

3 | TREATMENT ALGORITHM

The proposed algorithm for the treatment of AD is detailed in Figure 1.

3.1 | Identification and early management of AD

The severity of AD should be established based on clinical signs, the extent of the disease, and patient-reported symptoms to determine the appropriate treatment options. The SCORing Atopic Dermatitis (SCORAD) clinical tool allows an assessment of AD severity based on clinical signs, including erythema, edema/papulation, and oozing/crusts, as well as subjective symptoms (pruritus and sleep loss).[49] Early disease control, such as the use of emollients and avoidance of environmental triggers (e.g., food allergies), may prevent AD persisting into later life and possibly, the atopic march to allergic rhinitis and asthma.[50,51] Furthermore, the effective treatment of mild-to-moderate AD lesions can prevent patients developing a more severe form of the disease.[50,51]

Education programs for health-care professionals in multiple specialties can ensure timely identification and diagnosis of AD, for instance, training for general practitioners to refer patients with a history of AD to a physician experienced in management of AD. In addition, workshop-style sessions could be established in health-care settings to educate patients and their families about AD and lifelong management.

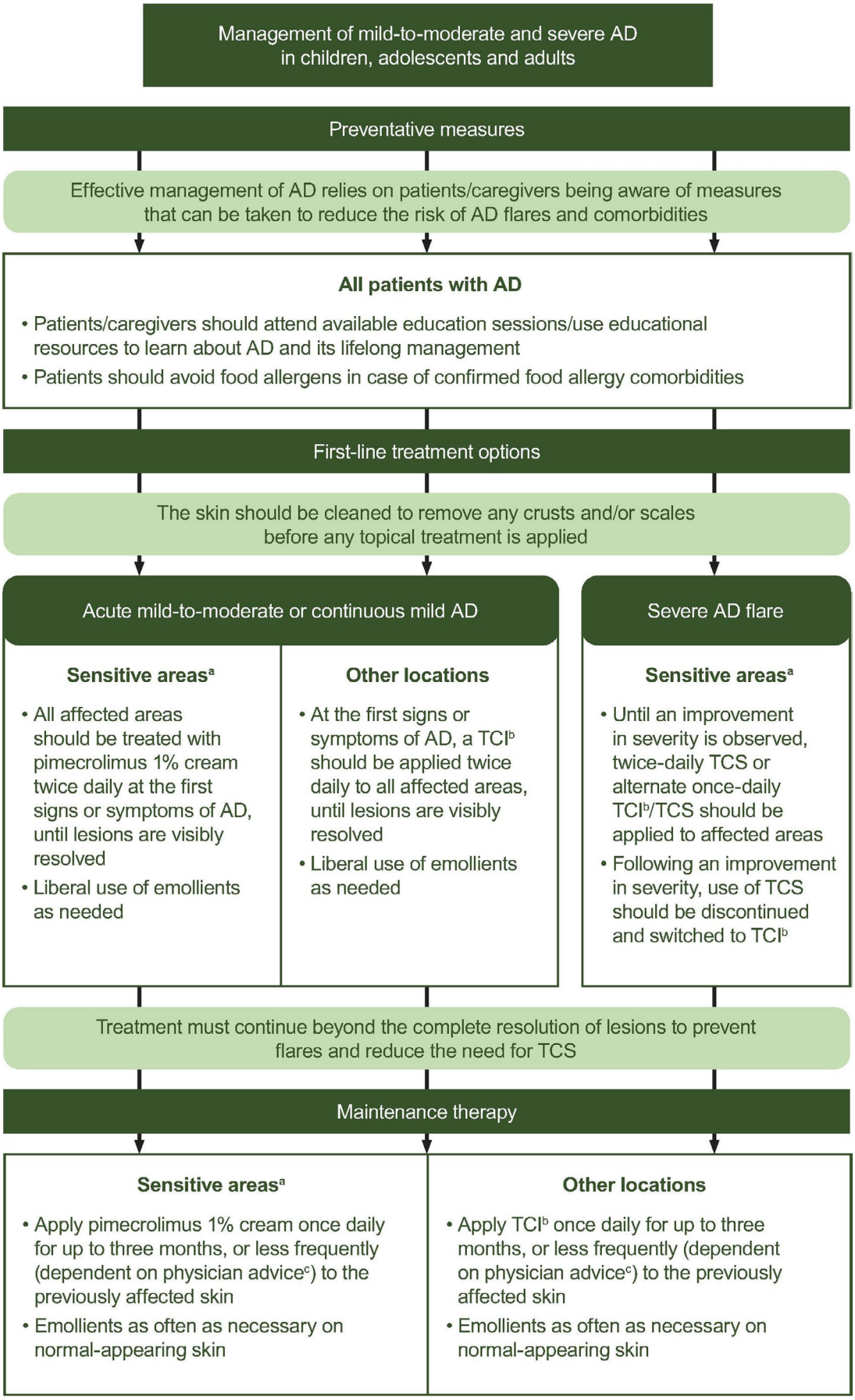
3.2 | First-line treatment according to proposed algorithm: mild-to-moderate AD

The topical calcineurin inhibitors (TCI) pimecrolimus and tacrolimus are licensed for the treatment of AD.[44,52–54] Tacrolimus 0.03% ointment is approved for the treatment of moderate-to-severe AD in patients aged 2–15 years, and tacrolimus 0.1% ointment for the treatment of patients aged 16 years or more. Pimecrolimus 1% cream is generally approved for mild-to-moderate AD in adults and children aged 2 years or more, but is also approved for use in infants aged 3 months or more in Australia, Brazil, Canada, India, Indonesia, Israel, New Zealand, the Philippines, Russia, and Thailand.[55–65] However, pimecrolimus is not available in some countries, including Japan. In the European atopic eczema (AD) guidelines, pimecrolimus is the preferred TCI for the treatment of facial lesions and children (according to overall recommendations), with tacrolimus recommended for long-term maintenance treatment.[44]

In non-sensitive body locations, either pimecrolimus or tacrolimus are recommended for use (Figure 1). Patients with mild-to-moderate AD aged 2–15 years treated with tacrolimus 0.03% ointment showed a significantly greater percent improvement in Eczema Area and Severity Index (EASI) scores compared with vehicle ointment (54.8% vs. 20.8%), alongside improvements in the total body surface area affected by AD and a lower itch score in the tacrolimus group.[66] Pimecrolimus 1% cream has been shown to reduce the number of AD flares and increase the median time to first AD flare when compared with a vehicle cream control (144 vs. 26 days, $p < 0.001$).[67]

While both TCI are preferred over topical corticosteroid (TCS) for the treatment of sensitive skin areas, pimecrolimus is preferred over tacrolimus for use in sensitive areas.[68] Sensitive areas include the head, face (eyelids and perioral region), neck, axilla region, inguinal folds, and genital area. In direct head-to-head comparisons of topical pimecrolimus with tacrolimus, pimecrolimus demonstrated greater efficacy in reducing the signs and symptoms of AD in sensitive skin areas, specifically in the head and neck region (54% reduction in AD with pimecrolimus treatment vs. 35% with tacrolimus treatment; treatment difference not significant).[69] Alongside these results, local erythema was less common and was experienced for a shorter duration of time in patients being treated with pimecrolimus than with tacrolimus.[69] TCI do not impair the skin barrier and may even be able to restore barrier function in damaged skin.[70,71] Systemic exposure is lower for pimecrolimus than tacrolimus, making it more suitable for patients with extensive lesions and in children, as systemic absorption is minimized.[72,73] This difference in systemic absorption is due to pimecrolimus being more lipophilic with a greater binding affinity for skin proteins and lower skin permeability.[74,75] The use of pimecrolimus 1% cream was well tolerated and demonstrated marked improvements in treating patients with Netherton syndrome, even when applied to 50% of the total body surface area.[76] In contrast to tacrolimus, pimecrolimus systemic absorption in children with Netherton syndrome is very low after 4 weeks of treatment resulting in a significant improvement of the skin lesions.[76] Pimecrolimus has a selective action on T lymphocytes, mast cells and basophils, and, unlike tacrolimus, has no action on Langerhans cells.[77–79]

Skin burning is a common adverse event following TCI application;[80,81] within the clinic, this usually occurs in the first 3 days of treatment. Based on clinical experience, cooling the product in the refrigerator for 15–20 min before application may help to reduce the sensation of burning at the application site or, in adults, administrating oral acetylsalicylic acid 1 h prior to treatment for the first 3 days may help avoid or alleviate burning.[82,83] A shorter duration of warmth, stinging, and burning reactions was reported in patients treated with pimecrolimus compared with those treated with tacrolimus. Although the incidence of these specific application site reactions was similar between groups in this particular study,[69] the incidence of burning sensations experienced by patients treated with pimecrolimus in clinical trials has been found to be generally low (~7–10%),[84,85] whereas tacrolimus-treated patients may experience a high incidence (36–50%) of application-site burning.[81,84,86]


Management of mild-to-moderate and severe AD in children, adolescents and adults
Preventative measures
Effective management of AD relies on patients/caregivers being aware of measures that can be taken to reduce the risk of AD flares and comorbidities
All patients with AD
• Patients/caregivers should attend available education sessions/use educational resources to learn about AD and its lifelong management
• Patients should avoid food allergens in case of confirmed food allergy comorbidities
First-line treatment options
The skin should be cleaned to remove any crusts and/or scales before any topical treatment is applied
Acute mild-to-moderate or continuous mild AD
Sensitive areas[a]
• All affected areas should be treated with pimecrolimus 1% cream twice daily at the first signs or symptoms of AD, until lesions are visibly resolved
• Liberal use of emollients as needed
Other locations
• At the first signs or symptoms of AD, a TCI[b] should be applied twice daily to all affected areas, until lesions are visibly resolved
• Liberal use of emollients as needed
Severe AD flare
Sensitive areas[a]
• Until an improvement in severity is observed, twice-daily TCS or alternate once-daily TCI[b]/TCS should be applied to affected areas
• Following an improvement in severity, use of TCS should be discontinued and switched to TCI[b]
Treatment must continue beyond the complete resolution of lesions to prevent flares and reduce the need for TCS
Maintenance therapy
Sensitive areas[a]
• Apply pimecrolimus 1% cream once daily for up to three months, or less frequently (dependent on physician advice[c]) to the previously affected skin
• Emollients as often as necessary on normal-appearing skin
Other locations
• Apply TCI[b] once daily for up to three months, or less frequently (dependent on physician advice[c]) to the previously affected skin
• Emollients as often as necessary on normal-appearing skin

3.3 | First-line treatment according to proposed algorithm: severe AD flares

For severe AD flares in sensitive skin areas, TCS can be used as initial treatment until an improvement in severity has been observed (Figure 1). Alternatively, once-daily TCS/TCI can be used in alternate until an improvement in severity is observed (Figure 1). Following an improvement in severity, TCS use should be discontinued and switched to TCI. Although TCS are effective for the short-term treatment of AD,[85,87,88] long-term use is not recommended. Application to sensitive areas should be minimized due to potential side-effects,[89] particularly as the increased skin permeation of TCS, relative to pimecrolimus, increases the risks of side-effects.[74] Side-effects associated with TCS include local cutaneous events (e.g., impairment of epidermal barrier function,[70,90] skin atrophy, and acne) and systemic effects (e.g., hypothalamic–pituitary–adrenal axis suppression).[88,89] Awareness and fear of these side-effects, or corticophobia, is common in several European and Asian countries[91–96] and is associated with non-adherence to treatment.[95,97,98]

3.4 | Management of AD in infants

Early treatment of AD during infancy and early childhood may reduce the progression of AD and prevent atopic march.[50] Emollients are an important part of treatment, and long-term use of emollients has demonstrated preventative effects in infants who are at risk of developing AD.[50,51]

Topical calcineurin inhibitors are an effective treatment option in infants with mild-to-moderate AD,[55,99] although only pimecrolimus is currently approved for use in children under 2 years of age in certain countries, for example, Russia.[55] Comprehensive evidence of the clinical efficacy and safety of pimecrolimus in infants and children comes from nine studies that were conducted in more than 6700 patients (including 4799 infants and 1312 children).[85,100–107] For example, results from the Petite study support the safe and efficacious long-term use of pimecrolimus in infants with mild-to-moderate AD with short-term use of TCS as rescue therapy during AD flares;[105] this study enrolled 2418 infants with up to 5 years of follow-up.[105] Similarly, over a period of 2 years in an open-label phase 2 study of 50 infants, treatment with tacrolimus 0.03% ointment resulted in substantial clinical improvement of AD, with similar tolerability as reported in older children.[108]

3.5 | Maintenance treatment for AD

Maintenance treatments are important to prevent flares and reduce TCS use. Pimecrolimus is the recommended TCI for maintenance treatment for sensitive skin in the algorithm proposed, and either tacrolimus or pimecrolimus may be used as maintenance therapy for other areas of the body (Figure 1). Both pimecrolimus and tacrolimus have demonstrated clinical benefits as maintenance treatments for AD. Proactive treatment with tacrolimus 0.1% ointment significantly reduced the number of disease exacerbations (DE) requiring substantial therapeutic intervention (median difference, 2; $p < 0.001$) and the proportion of DE treatment days (median difference, 15.2%; $p < 0.001$), as well as increasing the time to first DE (142 vs. 15 days; $p < 0.001$) when compared with vehicle ointment in a 12-month study.[109] Following 16 weeks of maintenance treatment with pimecrolimus, the disease relapse rate was reduced in patients receiving once- and twice-daily applications (14.7% and 9.9%, respectively).[110] Furthermore, a 12-month efficacy study of pimecrolimus treatment at the early signs of AD, showed a significant reduction in the incidence of flares (67.6% vs. 30.4%, $p < 0.001$) and an improvement in the overall control of AD when treated with pimecrolimus compared with vehicle.[106] Long-term safety data for TCI, together with guideline recommendations, support the use of pimecrolimus as the preferred treatment option for sensitive skin areas.[44,111] Currently, there is no evidence that proactive treatment is superior to treatment started at the first signs and symptoms, usually itch, of a new AD flare. Proactive treatment with TCS may also be considered for patients with frequent flares, as there is evidence to indicate that using TCS plus emollients as maintenance therapy is more effective for preventing relapses compared with emollients alone.[41,112] Regular use of emollients in AD is recommended as epidermal barrier dysfunction can negatively affect skin hydration and increase transepidermal water loss.[113,114]

3.6 | Novel topical therapies for AD

Crisaborole ointment is a topical phosphodiesterase-4 inhibitor used for the treatment of mild-to-moderate AD,[115] which is currently approved in a limited number of countries. A pooled analysis of clinical data showed that crisaborole 2% ointment significantly reduced the severity of pruritus compared with treatment with vehicle.[115] Safety analyses showed crisaborole 2% ointment to be well tolerated, with the most commonly reported treatment-related adverse events being application site pain, pruritus, and dermatitis.[115] Microbiome-targeting treatments are being developed due to the promising results of a phase 1/2 trial investigating treatment with topical *Roseomonas mucosa*. In this study, significant decreases in AD severity, TCS requirements, and *S. aureus* burden were observed following treatment with *R. mucosa* in patients with AD.[116] Janus kinase (JAK), a family of tyrosine kinases, has been implicated in AD, with inhibition of JAK resulting in sustained anti-pruritic effects.[117]

FIGURE 1 Algorithm for the topical treatment of atopic dermatitis in children, adolescents, and adults. [a]These areas include the head, face (eyelids and perioral region), neck, axilla region, inguinal folds, and genital area. In these areas, a cream is preferred to an ointment. [b]Pimecrolimus 1% cream for all ages; tacrolimus 0.1% ointment for adults; tacrolimus 0.03% ointment for children. Pimecrolimus is indicated for mild-to-moderate AD and tacrolimus is indicated for moderate-to-severe AD.[55,124c] Not included in the Summary of Product Characteristics for pimecrolimus. Abbreviations: AD, atopic dermatitis; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid

In a recent phase 2 trial in patients with AD, treatment with ruxolitinib cream, a potent JAK1/JAK2 inhibitor, significantly improved EASI score versus vehicle cream at week 4 (71.6% improvement vs. 15.5%, $p < 0.001$).[118] Treatment with topical ruxolitinib also significantly improved the Investigators Global Assessment (IGA) score and pruritus compared with vehicle at week 4.[118] Another JAK inhibitor, delgocitinib, has been approved in Japan for topical use in patients with AD.[119] In both phase 2 and phase 3 trials in Japanese patients with AD, delgocitinib demonstrated significantly reduced modified EASI scores versus vehicle ointment after 4 weeks.[120,121] Tapinarof is a topical aryl hydrocarbon receptor agonist that has been investigated in patients with AD.[122] In a recent study, the rate of treatment success (minimum 2-grade IGA score improvement) with tapinarof cream at week 12 was shown to range from 34% to 53% (dose dependent) and was significantly higher than that with vehicle treatment (24%).[122] It should be noted that some of these novel treatments are costly, which may limit their use. The treatments recommended in the proposed algorithm (Figure 1) are economical[123] and effective for the management of AD.

4 | CONCLUSIONS

The proposed treatment algorithm should help guide physicians in clinical practice when treating patients with mild-to-moderate AD and those with severe flares. According to the algorithm, pimecrolimus is the preferred TCI for application on sensitive skin areas due to its efficacy, tolerability, and selectivity profile compared with tacrolimus. However, both pimecrolimus and tacrolimus are recommended for other areas of the body. TCS are recommended for short-term use only in cases of severe flares due to their side-effects, such as thinning of the epidermal barrier. This treatment algorithm can help guide clinical decision-making in the treatment of AD, potentially reducing the burden of AD for patients, their families, and health-care systems.

ACKNOWLEDGMENTS

Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Zoe Schafer, Sam McCracken, and Jane Murphy, of Ashfield MedComms, an Ashfield Health company, and funded by Meda Pharma S.p.A., *a Viatris company*.

CONFLICT OF INTEREST

T.L. has participated as principal investigator in clinical trials and advisory boards, and has given lectures, sponsored by Viatris, Novartis, Lilly, Pfizer, Janssen, and Sanofi. He has received consultancy/speaker honoraria from Novartis, Abbvie, Galderma, La Roche Posay, Viatris, Janssen, and Sanofi, and has acted as a scientific advisory board member for Abbvie, Celgene, La Roche Posay, Janssen, Pfizer, Menlo, Viatris, Galderma, Symrise, Sandoz, and Lilly. He has received research grants from Celgene, Janssen-Cilag, Leo, Viatris, and Pfizer. U.A. has nothing to disclose. M.A. has participated in an advisory board sponsored by Loreal. She has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatris company*), Loreal, Bayer, Delta Medical, and Bausch Health. X.D. has nothing to disclose. N.N.M. has participated as a principal investigator in clinical trials sponsored by Novartis, Lilly, and Janssen. He has received consultancy/speaker honoraria from Abbvie, Bayer, Galderma, Pierre Fabre, Pfizer, Leo Pharma, Meda Pharma S.p.A. (*a Viatris company*), and Janssen Pharmaceutical, and has acted as a scientific advisory board member for Meda Pharma S.p.A. (*a Viatris company*), Galderma, and Pierre Fabre. L.N.B. has received research grants and consultancy/speaker honoraria from pharmaceutical companies Pierre Fabre, Genzyme Europe B. V, AstraZeneca Pharmaceuticals LLC, Gilead/PRA Pharmaceutical Research Associates CIS, Bionorica, Teva Branded Pharmaceutical Products R&D Inc/PPD Development LLC (Smolensk), Stallergen C.A./Quintiles Geismbh (Austria), MSD, Pfizer, Abbvie, Galderma, Meda Pharma S.p.A. (*a Viatris company*), Sanofi, Astellas, and Takeda (formerly Shire). O.N. has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatris company*), Nestle, and Delta Medical. A.R. has nothing to disclose. T.V.S. reports that she has received consultancy/speaker honoraria from Meda Pharma S.p.A. (*a Viatris company*) and Dr. Reddy's Laboratories. Z.T. has received consultancy/speaker honoraria from Numil and Sandoz, and acted as scientific advisory board member for Numil and Meda Pharma S.p.A. (*a Viatris company*). M.T. has nothing to disclose. E.A.V. has participated as a principal investigator in clinical trials sponsored by Sanofi. She has received research grants and consultancy/speaker honoraria from Abbvie, AstraZeneca, Meda Pharma S.p.A. (*a Viatris company*), MSD, Novartis, Sandoz and Stallergenes Greer, and has acted as scientific advisory board member for Meda Pharma S.p.A. (*a Viatris company*), MSD, Pfizer, Sanofi, Stallergenes Greer, and Takeda (formerly Shire). S.V. has nothing to disclose. H.W. has acted as scientific advisory board member for LEO, Meda Pharma S.p.A. (*a Viatris company*) and Sanofi. Z.Z. has participated as a principal investigator in clinical trials sponsored by Novartis and Pfizer. He has received consultancy/speaker honoraria from Novartis, Pfizer, Astellas, Galderma, Janssen, GSK, BAYER, LEO, and Meda Pharma S.p.A. (*a Viatris company*), and has acted as a scientific advisory board member for Pfizer, Novartis, Astellas, LEO, and Meda Pharma S.p.A. (*a Viatris company*). He has received research grants from Astellas, Pfizer, Novartis, and ALK Pharma.

ORCID

Thomas Luger https://orcid.org/0000-0003-1397-1626

REFERENCES

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387:1109–22.
2. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66(Suppl 1):8–16.
3. Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson R, *et al*. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. *J Allergy Clin Immunol*. 1999;103:125–38.

4. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol*. 2008;121:947–54.e15.
5. Xu F, Yan S, Li F, Cai M, Chai W, Wu M, *et al*. Prevalence of childhood atopic dermatitis: an urban and rural community-based study in Shanghai, China. *PLoS One*. 2012;7:e36174.
6. Guo Y, Li P, Tang J, Han X, Zou X, Xu G, *et al*. Prevalence of atopic dermatitis in Chinese children aged 1–7 ys. *Sci Rep*. 2016;6:29751.
7. Dogruel D, Bingol G, Altintas DU, Seydaoglu G, Erkan A, Yilmaz M. The trend of change of allergic diseases over the years: three repeated surveys from 1994 to 2014. *Int Arch Allergy Immunol*. 2017;173:178–82.
8. Kryuchko TO, Holovanova IA, Tkachenko OY, Melnyk MO, Pocheniuk KV. Prevalence of risk factors of allergic diseases among children aged 8–9 years in poltava region (the results of the first stage of the research). *Wiad Lek*. 2018;71:699–704.
9. Shpakou A, Brozek G, Stryzhak A, Neviartovich T, Zejda J. Allergic diseases and respiratory symptoms in urban and rural children in Grodno Region (Belarus). *Pediatr Allergy Immunol*. 2012;23:339–46.
10. Murashkin NN, Ambarchian ET, Materikin AI, Epishev RV. The role of epidermal barrier impairments in atopic dermatitis: modern concepts of disease pathogenesis. *Current pediatrics*. 2018;17:85–8. https://doi.org/10.15690/vsp.v17i1.1859
11. Kubanova AA, Kubanov AA, Melekhina LE, Bogdanova EV. The assessment of the incidence of skin disorders in Russian Federation in 2003–2016. *Vestn Dermatol Venerol*. 2017;93:22–33.
12. Namazova-Baranova LS, Ogorodova L, Tomilova A, Deev I, Alekseeva A, Vishneva E, *et al*. Prevalence of asthma-like symptoms and diagnosed asthma in the population of adolescents. *Pediatr Pharmacol*. 2009;6:59–65.
13. Brunner PM, Guttman-Yassky E, Leung DYM. The immunology of AD and its reversibility with broad spectrum and targeted therapies. *J Allergy Clin Immunol*. 2017;139:S65–S76.
14. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143:1–11.
15. van Neerven RJJ, Savelkoul H. Nutrition and allergic diseases. *Nutrients*. 2017;9:762.
16. Penders J, Stobberingh EE, Thijs C, Adams H, Vink C, van Ree R, *et al*. Molecular fingerprinting of the intestinal microbiota of infants in whom atopic eczema was or was not developing. *Clin Exp Allergy*. 2006;36:1602–8.
17. Nakatsuji T, Chen TH, Narala S, Chun KA, Two AM, Yun T, *et al*. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9:eaah4680.
18. Wollina U. Microbiome in atopic dermatitis. *Clin Cosmet Investig Dermatol*. 2017;10:51–6.
19. Lee S-Y, Lee E, Park YM, Hong S-J. Microbiome in the gut-skin axis in atopic dermatitis. *Allergy Asthma Immunol Res*. 2018;10:354–62.
20. Kong HH, Oh J, Deming C, Conlan S, Grice EA, Beatson MA, *et al*. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res*. 2012;22:850–9.
21. Anderson SE, Weatherly L, Shane HL. Contribution of antimicrobials to the development of allergic disease. *Curr Opin Immunol*. 2019;60:91–5.
22. Mitre E, Susi A, Kropp LE, Schwartz DJ, Gorman GH, Nylund CM. Association between use of acid-suppressive medications and antibiotics during infancy and allergic diseases in early childhood. *JAMA Pediatr*. 2018;172:e180315.
23. Byrd AL, Deming C, Cassidy SKB, Harrison OJ, Ng W-I, Conlan S, *et al*. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med*. 2017;9:eaal4651.
24. Flohr C, Mann J. New insights into the epidemiology of childhood atopic dermatitis. *Allergy*. 2014;69:3–16.
25. Katta R, Schlichte M. Diet and dermatitis: food triggers. *J Clin Aesthet Dermatol*. 2014;7:30–6.
26. Dhar S, Srinivas SM. Food allergy in atopic dermatitis. *Indian J Dermatol*. 2016;61:645–8.
27. Natsume O, Ohya Y. Recent advancement to prevent the development of allergy and allergic diseases and therapeutic strategy in the perspective of barrier dysfunction. *Allergol Int*. 2018;67:24–31.
28. Lavery WJ, Assa'ad A. How to prevent food allergy during infancy: what has changed since 2013? *Curr Opin Allergy Clin Immunol*. 2018;18:265–70.
29. Chernyshov PV. Gender differences in health-related and family quality of life in young children with atopic dermatitis. *Int J Dermatol*. 2012;51:290–4.
30. Chernyshov PV, Jirakova A, Ho RCM, Moed H, Caldeira AP, Alvarenga TM, *et al*. An international multicenter study on quality of life and family quality of life in children with atopic dermatitis. *Indian J Dermatol Venereol Leprol*. 2013;79:52–8.
31. 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;19:821–38.
32. Bridgman AC, Eshtiaghi P, Cresswell-Melville A, Ramien M, Drucker AM. The burden of moderate to severe atopic dermatitis in Canadian children: a Cross-Sectional Survey. *J Cutan Med Surg*. 2018;22:443–4.
33. Kuniyoshi Y, Kikuya M, Miyashita M, Yamanaka C, Ishikuro M, Obara T, *et al*. Severity of eczema and mental health problems in Japanese schoolchildren: the ToMMo Child Health Study. *Allergol Int*. 2018;67:481–6.
34. Kwak Y, Kim Y. Health-related quality of life and mental health of adults with atopic dermatitis. *Arch Psychiatr Nurs*. 2017;31:516–21.
35. Komata T, Ebisawa M. The importance of early diagnosis and treatment of infantile atopic dermatitis associated with food allergy. *J Allergy Clin Immun*. 2009;123:S190.
36. Thomsen SF. Atopic dermatitis: natural history, diagnosis, and treatment. *ISRN Allergy*. 2014;2014:354250.
37. Ong PY, Leung DY. Bacterial and viral infections in atopic dermatitis: a comprehensive review. *Clin Rev Allergy Immunol*. 2016;51:329–37.
38. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: a systematic review of epidemiological studies. *PLoS One*. 2012;7:e39803.
39. Katayama I, Aihara M, Ohya Y, Saeki H, Shimojo N, Shoji S, *et al*. Japanese guidelines for atopic dermatitis 2017. *Allergol Int*. 2017;66:230–47.
40. Akdis CA, Akdis M, Bieber T, Bindslev-Jensen C, Boguniewicz M, Eigenmann P, *et al*. Diagnosis and treatment of atopic dermatitis in children and adults: European Academy of Allergology and Clinical Immunology/American Academy of Allergy, Asthma and Immunology/PRACTALL Consensus Report. *J Allergy Clin Immunol*. 2006;118:152–69.
41. Darsow U, Wollenberg A, Simon D, Taïeb A, Werfel T, Oranje A, *et al*. ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 2010;24:317–28.
42. Kim JE, Kim HJ, Lew B-L, Lee KH, Hong SP, Jang YH, *et al*. Consensus guidelines for the treatment of atopic dermatitis in Korea (Part I): general management and topical treatment. *Ann Dermatol*. 2015;27:563–77.
43. Eichenfield LF, Boguniewicz M, Simpson EL, Russell JJ, Block JK, Feldman SR, *et al*. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics*. 2015;136:554–65.

44. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, *et al*. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I. *J Eur Acad Dermatol Venereol*. 2018;32:657–82.
45. Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, Fink-Wagner A, *et al*. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol*. 2018;32:850–78.
46. Namazova-Baranova LS, Baranov AA, Kubanova AA, Ilina NI, Kurbacheva OM, Vishneva EA, *et al*. Atopic dermatitis in children: current clinical guidelines for diagnosis and therapy. *Current Pediatrics*. 2016;15:279–94.
47. Reda AM, Elgendi A, Ebraheem AI, Aldraibi MS, Qari MS, Abdulghani MMR, *et al*. A practical algorithm for topical treatment of atopic dermatitis in the Middle East emphasizing the importance of sensitive skin areas. *J Dermatolog Treat*. 2019;30:366–73.
48. Luk D, Hon KLE, Dizon MVC, Leong K-F, Tay Y-K, Koh MJ-A, *et al*. Practical recommendations for the topical treatment of atopic dermatitis in South and East Asia. *Dermatol Ther*. 2021;11:275–91. https://doi.org/10.1007/s13555-13020-00467-13558
49. Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology*. 1993;186:23–31.
50. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WHI, *et al*. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134:818–23.
51. Glatz M, Jo J-H, Kennedy EA, Polley EC, Segre JA, Simpson EL, *et al*. Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS One*. 2018;13:e0192443.
52. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, *et al*. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol*. 2012;26:1045–60.
53. Werfel T, Schwerk N, Hansen G, Kapp A. The diagnosis and graded therapy of atopic dermatitis. *Dtsch Arztebl Int*. 2014;111:509–20.
54. Sidbury R, Davis DM, Cohen DE, Cordoro KM, Berger TG, Bergman JN, *et al*. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Dermatol*. 2014;71:327–49.
55. Luger T, Boguniewicz M, Carr W, Cork M, Deleuran M, Eichenfield L, *et al*. Pimecrolimus in atopic dermatitis: consensus on safety and the need to allow use in infants. *Pediatr Allergy Immunol*. 2015;26:306–15.
56. Mylan. Elidel 1% Summary of Product Characteristics (Thailand). April 2008 [Cited 2021 January].
57. Mylan. Elidel 1% Summary of Product Characteristics (New Zealand). April 2018 [Cited 2021 January].
58. Mylan. Elidel 1% Summary of Product Characteristics (Australia). May 2018 [Accessed 2021 January 18]. https://medicines.org.au/i/view/gopelidePI
59. Valeant. Elidel 1% Product Monograph (Canada). September 2019 [Cited 2021 January].
60. Mylan. Elidel 1% Summary of Product Characteristics (Philippines). April 2017 [Cited 2021 January].
61. Mylan. Elidel 1% Summary of Product Characteristics (India). May 2018 [Cited 2021 January].
62. Mylan. Elidel 1% Summary of Product Characteristics (Indonesia). April 2008 [Cited 2021 January].
63. Mylan. Elidel 1% Prescribing Information (Russia). [Accessed 2021 January 18]. https://diateza.net/upload/doc/elidel.pdf
64. Mylan. Elidel 1% Prescribing Information (Israel). September 2009 [Accessed 2021 January 18]. https://data.health.gov.il/drugs/alonim/Elidel_dr_1328699572985.pdf.
65. Mylan. Elidel 1% Summary of Product Characteristics (Brazil). November 2018 [Cited 2021 January].
66. Schachner LA, Lamerson C, Sheehan MP, Boguniewicz M, Mosser J, Raimer S, *et al*. Tacrolimus ointment 0.03% is safe and effective for the treatment of mild to moderate atopic dermatitis in pediatric patients: results from a randomized, double-blind, vehicle-controlled study. *Pediatrics*. 2005;116:e334–e342.
67. Meurer M, Fölster-Holst R, Wozel G, Weidinger G, Jünger M, Bräutigam M, *et al*. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology*. 2002;205:271–7.
68. Luger T, De Raeve L, Gelmetti C, Kakourou T, Katsarou A, Lambert J, *et al*. Recommendations for pimecrolimus 1% cream in the treatment of mild-to-moderate atopic dermatitis: from medical needs to a new treatment algorithm. *Eur J Dermatol*. 2013;23:758–66.
69. Kempers S, Boguniewicz M, Carter E, Jarratt M, Pariser D, Stewart D, *et al*. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol*. 2004;51:515–25.
70. Jensen J-M, Pfeiffer S, Witt M, Bräutigam M, Neumann C, Weichenthal M, *et al*. Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2009;124:R19–28.
71. Reitamo S, Rissanen J, Remitz A, Granlund H, Erkko P, Elg P, *et al*. Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol*. 1998;111:396–8.
72. Allen BR, Lakhanpaul M, Morris A, Lateo S, Davies T, Scott G, *et al*. Systemic exposure, tolerability, and efficacy of pimecrolimus cream 1% in atopic dermatitis patients. *Arch Dis Child*. 2003;88:969–73.
73. Draelos Z, Nayak A, Pariser D, Shupack JL, Chon K, Abrams B, *et al*. Pharmacokinetics of topical calcineurin inhibitors in adult atopic dermatitis: a randomized, investigator-blind comparison. *J Am Acad Dermatol*. 2005;53:602–9.
74. Billich A, Aschauer H, Aszodi A, Stuetz A. Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus. *Int J Pharm*. 2004;269:29–35.
75. Weiss HM, Fresneau M, Moenius T, Stuetz A, Billich A. Binding of pimecrolimus and tacrolimus to skin and plasma proteins: implications for systemic exposure after topical application. *Drug Metab Dispos*. 2008;36:1812–8.
76. Yan AC, Honig PJ, Ming ME, Weber J, Shah KN. The safety and efficacy of pimecrolimus, 1%, cream for the treatment of Netherton syndrome: results from an exploratory study. *Arch Dermatol*. 2010;146:57–62.
77. Panhans-Gross A, Novak N, Kraft S, Bieber T. Human epidermal Langerhans' cells are targets for the immunosuppressive macrolide tacrolimus (FK506). *J Allergy Clin Immunol*. 2001;107:345–52.
78. Hoetzenecker W, Ecker R, Kopp T, Stuetz A, Stingl G, Elbe-Burger A. Pimecrolimus leads to an apoptosis-induced depletion of T cells but not Langerhans cells in patients with atopic dermatitis. *J Allergy Clin Immunol*. 2005;115:1276–83.
79. Zuberbier T, Chong S-U, Grunow K, Guhl S, Welker P, Grassberger M, *et al*. The ascomycin macrolactam pimecrolimus (Elidel, SDZ ASM 981) is a potent inhibitor of mediator release from human dermal mast cells and peripheral blood basophils. *J Allergy Clin Immunol*. 2001;108:275–80.
80. Broeders JA, Ahmed Ali U, Fischer G. Systematic review and meta-analysis of randomized clinical trials (RCTs) comparing topical calcineurin inhibitors with topical corticosteroids for atopic dermatitis: A 15-year experience. *J Am Acad Dermatol*. 2016;75:410–9.e413.
81. Seo SR, Lee SG, Lee HJ, Yoon MS, Kim DH. Disrupted skin barrier is associated with burning sensation after topical tacrolimus application in atopic dermatitis. *Acta Derm Venereol*. 2017;97:957–8.

82. Mandelin J, Remitz A, Reitamo S. Effect of oral acetylsalicylic acid on burning caused by tacrolimus ointment in patients with atopic dermatitis. *Arch Dermatol*. 2010;146:1178–80.
83. Al-Khenaizan S. Practical tip: precooling topical calcineurin inhibitors tube; reduces burning sensation. *Dermatol Online J*. 2010;16:16.
84. Lynde C, Barber K, Claveau J, Gratton D, Ho V, Krafchik B, *et al*. Canadian practical guide for the treatment and management of atopic dermatitis. *J Cutan Med Surg*. 2005;8:1–9.
85. Ring J, Abraham A, de Cuyper C, Kim K, Langeland T, Parra V, *et al*. Control of atopic eczema with pimecrolimus cream 1% under daily practice conditions: results of a > 2000 patient study. *J Eur Acad Dermatol Venereol*. 2008;22:195–203.
86. Reitamo S, Wollenberg A, Schöpf E, Perrot JL, Marks R, Ruzicka T, *et al*. Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. The European Tacrolimus Ointment Study Group. *Arch Dermatol*. 2000;136:999–1006.
87. Wollenberg A, Oranje A, Deleuran M, Simon D, Szalai Z, Kunz B, *et al*. ETFAD/EADV Eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and paediatric patients. *J Eur Acad Dermatol Venereol*. 2016;30:729–47.
88. Watson W, Kapur S. Atopic dermatitis. *Allergy Asthma Clin Immunol*. 2011;7:S4.
89. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ. Adverse effects of topical glucocorticosteroids. *J Am Acad Dermatol*. 2006;54:1–15; quiz 16–18.
90. Queille-Roussel C, Paul C, Duteil L, Lefebvre MC, Rapatz G, Zagula M, *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;144:507–13.
91. Hon KL, Leung TF, Yau HC, Chan T. Paradoxical use of oral and topical steroids in steroid-phobic patients resorting to traditional Chinese medicines. *World J Pediatr*. 2012;8:263–7.
92. Song SY, Jung SY, Kim E. Steroid phobia among general users of topical steroids: a cross-sectional nationwide survey. *J Dermatolog Treat*. 2019;30:245–50.
93. Li Y, Han T, Li W, Li Y, Guo X, Zheng L. Awareness of and phobias about topical corticosteroids in parents of infants with eczema in Hangzhou, China. *Pediatr Dermatol*. 2018;35:463–7.
94. Raffin D, Giraudeau B, Samimi M, Machet L, Pourrat X, Maruani A. Corticosteroid phobia among pharmacists regarding atopic dermatitis in children: a National French Survey. *Acta Derm Venereol*. 2016;96:177–80.
95. El Hachem M, Gesualdo F, Ricci G, Diociaiuti A, Giraldi L, Ametrano O, *et al*. Topical corticosteroid phobia in parents of pediatric patients with atopic dermatitis: a multicentre survey. *Ital J Pediatr*. 2017;43:22.
96. Mueller SM, Itin P, Vogt DR, Walter M, Lang U, Griffin LL, *et al*. Assessment of "corticophobia" as an indicator of non-adherence to topical corticosteroids: a Pilot Study. *J Dermatolog Treat*. 2017;28:104–11.
97. Charman CR, Morris AD, Williams HC. Topical corticosteroid phobia in patients with atopic eczema. *Br J Dermatol*. 2000;142:931–6.
98. Aubert-Wastiaux H, Moret L, Le Rhun A, Fontenoy AM, Nguyen JM, Leux C, *et al*. Topical corticosteroid phobia in atopic dermatitis: a study of its nature, origins and frequency. *Br J Dermatol*. 2011;165:808–14.
99. Chapman MS, Schachner LA, Breneman D, Boguniewicz M, Gold MH, Shull T, *et al*. Tacrolimus ointment 0.03% shows efficacy and safety in pediatric and adult patients with mild to moderate atopic dermatitis. *J Am Acad Dermatol*. 2005;53:S177–S185.
100. Staab D, Kaufmann R, Brautigam M, Wahn U. Treatment of infants with atopic eczema with pimecrolimus cream 1% improves parents' quality of life: a multicenter, randomized trial. *Pediatr Allergy Immunol*. 2005;16:527–33.
101. Papp KA, Werfel T, Fölster-Holst R, Ortonne J-P, Potter PC, de Prost Y, *et al*. Long-term control of atopic dermatitis with pimecrolimus cream 1% in infants and young children: a two-year study. *J Am Acad Dermatol*. 2005;52:240–6.
102. Kaufmann R, Fölster-Holst R, Höger P, Thaçi D, Löffler H, Staab D, *et al*. Onset of action of pimecrolimus cream 1% in the treatment of atopic eczema in infants. *J Allergy Clin Immunol*. 2004;114:1183–8.
103. Ho VC, Gupta A, Kaufmann R, Todd G, Vanaclocha F, Takaoka R, *et al*. Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *J Pediatr*. 2003;142:155–62.
104. Siegfried E, Korman N, Molina C, Kianifard F, Abrams K. Safety and efficacy of early intervention with pimecrolimus cream 1% combined with corticosteroids for major flares in infants and children with atopic dermatitis. *J Dermatolog Treat*. 2006;17:143–50.
105. Sigurgeirsson B, Boznanski A, Todd G, Vertruyen A, Schuttelaar M-LA, Zhu X, *et al*. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135:597–606.
106. Kapp A, Papp K, Bingham A, Fölster-Holst R, Ortonne J-P, Potter PC, *et al*. Long-term management of atopic dermatitis in infants with topical pimecrolimus, a nonsteroid anti-inflammatory drug. *J Allergy Clin Immunol*. 2002;110:277–84.
107. Hanifin JM, Boguniewicz M, Eichenfield LF, Schneider LC, Paller AS, Preston JA, *et al*. A long-term study of safety and allergic comorbidity development in a randomized trial of pimecrolimus cream in infants with atopic dermatitis. *J Invest Dermatol*. 2010;130:Abstract 328.
108. Mandelin JM, Rubins A, Remitz A, Cirule K, Dickinson J, Ho V, *et al*. Long-term efficacy and tolerability of tacrolimus 0.03% ointment in infants: *a two-year open-label study. *Int J Dermatol*. 2012;51:104–10.
109. Wollenberg A, Reitamo S, Girolomoni G, Lahfa M, Ruzicka T, Healy E, *et al*. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy*. 2008;63:742–50.
110. Ruer-Mulard M, Aberer W, Gunstone A, Kekki O-M, Estebaranz JLL, Vertruyen A, *et al*. Twice-daily versus once-daily applications of pimecrolimus cream 1% for the prevention of disease relapse in pediatric patients with atopic dermatitis. *Pediatr Dermatol*. 2009;26:551–8.
111. Siegfried EC, Jaworski JC, Kaiser JD, Hebert AA. Systematic review of published trials: long-term safety of topical corticosteroids and topical calcineurin inhibitors in pediatric patients with atopic dermatitis. *BMC Pediatr*. 2016;16:75.
112. Blume-Peytavi U, Metz M. Atopic dermatitis in children: management of pruritus. *J Eur Acad Dermatol Venereol*. 2012;26:2–8.
113. Tay YK, Chan YC, Chandran NS, Ho MSI, Koh MJ, Lim YL, *et al*. Guidelines for the management of atopic dermatitis in Singapore. *Ann Acad Med Singap*. 2016;45:439–50.
114. Leung TNH, Chow CM, Chow MPY, Luk DCK, Ho KM, Hon KL, *et al*. Clinical guidelines on management of atopic dermatitis in children. *Hong Kong J Paediatr*. 2013;18:96–104.
115. Zane LT, Chanda S, Jarnagin K, Nelson DB, Spelman L, Gold LS. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8:853–66.
116. Myles IA, Earland NJ, Anderson ED, Moore IN, Kieh MD, Williams KW, *et al*. First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis. *JCI Insight*. 2018;3:e120608.
117. He H, Guttman-Yassky E. JAK inhibitors for atopic dermatitis: an update. *Am J Clin Dermatol*. 2019;20:181–92.
118. BioSpace. Incyte Announces Positive Data from Phase 2b Trial of Ruxolitinib Cream in Patients with Atopic Dermatitis. 2018 [Cited 2020 September]. https://www.BioSpace.com/article/releases/incyte-announces-positive-data-from-phase-2b-trial-of-ruxolitinib-cream-in-patients-with-atopic-dermatitis/
119. Dhillon S. Delgocitinib: first approval. *Drugs*. 2020;80:609–15.

120. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. *J Am Acad Dermatol*. 2020;82:823–31.
121. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Oda M, Kabashima K, *et al*. Phase 2 clinical study of delgocitinib ointment in pediatric patients with atopic dermatitis. *J Allergy Clin Immunol*. 2019;144:1575–83.
122. Peppers J, Paller AS, Maeda-Chubachi T, Wu S, Robbins K, Gallagher K, *et al*. A phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2019;80:89–98.e83.
123. Chia BK, Tey HL. Systematic review on the efficacy, safety, and cost-effectiveness of topical calcineurin inhibitors in atopic dermatitis. *Dermatitis*. 2015;26:122–32.
124. LEO Pharma. Protopic (tacrolimus) prescribing information. LEO Pharma revised: 02/2019. Astellas Pharma. 2019. [Cited 2020 March 4]. http://www.protopic.com/

How to cite this article: Luger T, Adaskevich U, Anfilova M, et al. Practical algorithm to inform clinical decision-making in the topical treatment of atopic dermatitis. *J Dermatol*. 2021;00:1–10. https://doi.org/10.1111/1346-8138.15921