

New Perspectives in the Treatment of Atopic Dermatitis in the Pediatric Population

Luana Niculescu, MD,¹ Christoph Rothenberger, MD,¹ Melda Pinarci, MD,¹ Jelena Peric, MD, PhD,^{1,2}
Rehab Alharbi, MD,^{1,3} and Andreas Wollenberg, MD¹

Treatment of children diagnosed with atopic dermatitis (AD) is an art. Age-dependent barrier function, skin physiology, body surface:weight ratio, the compliance of patient and caregivers, and legal considerations related to the license status of topical and systemic drugs must be considered. Mild to moderate AD can usually be treated sufficiently with a personalized regimen of emollients and topical anti-inflammatory therapy consisting of topical corticosteroids (TCSs) or topical calcineurin inhibitors. Emollients containing bacterial lysates, tailored wet wrap regimen, and proactive therapy with tacrolimus ointment or some TCSs are new developments in the field. Severe AD may need systemic therapy, but all currently available systemic agents for severe AD are either not licensed for children or not advisable on the long term, or both. Therapeutic patient education based on structured, interactive sessions with patients or caregivers and a multidisciplinary team is highly effective. This publication summarizes the current therapeutic options used in the pediatric AD population.

Keywords: atopic dermatitis, children, proactive therapy, wet wrap, therapeutic patient education

Introduction

ATOPIC DERMATITIS (AD) is a highly pruritic, chronic inflammatory skin disease frequently affecting young children.^{1,2} Treatment of children must consider the age-dependent changes of barrier function and skin physiology, as well as the increased ratio of body surface and body weight of children and the frequently reduced compliance of young patients and their caregivers. Mild, moderate, and severe AD patients should all be treated with emollients at least once daily, together with an individualized anti-inflammatory treatment protocol. Mild to moderate AD can usually be treated sufficiently with a personalized regimen of emollients and topical anti-inflammatory therapy involving topical corticosteroids (TCSs) or topical calcineurin inhibitors (TCIs). As in adults, all systemic treatment of pediatric patients must be chosen carefully and individually,³ especially as there is no consented or even licensed standard therapy.² Most systemic therapies for childhood AD will, therefore, involve written informed consent before onset of medication.^{1,2}

Most current guidelines and position articles advising on AD treatment recommend a stepwise treatment escalation approach based on overall disease severity (Fig. 1). The latter must take objective signs and subjective symptoms into account, and therefore composite scores such as the

SCORAD⁴ or PO-SCORAD⁵ are recommended for assessing the overall disease severity.² The severity of AD can be classified by SCORAD values in a mild (<25), moderate (25–50), or severe (>50) course of the disease.⁶

The defective skin barrier leads to an increased penetration of environmental allergens and infectious agents. A persistent low level of inflammation and an increased transepidermal water loss are detectable in the seemingly normal, nonlesional AD skin, which is the basis for proactive treatment.^{7,8} This review summarizes the current topical and systemic treatment options recommended in the pediatric AD population.

Basic Topical Therapy

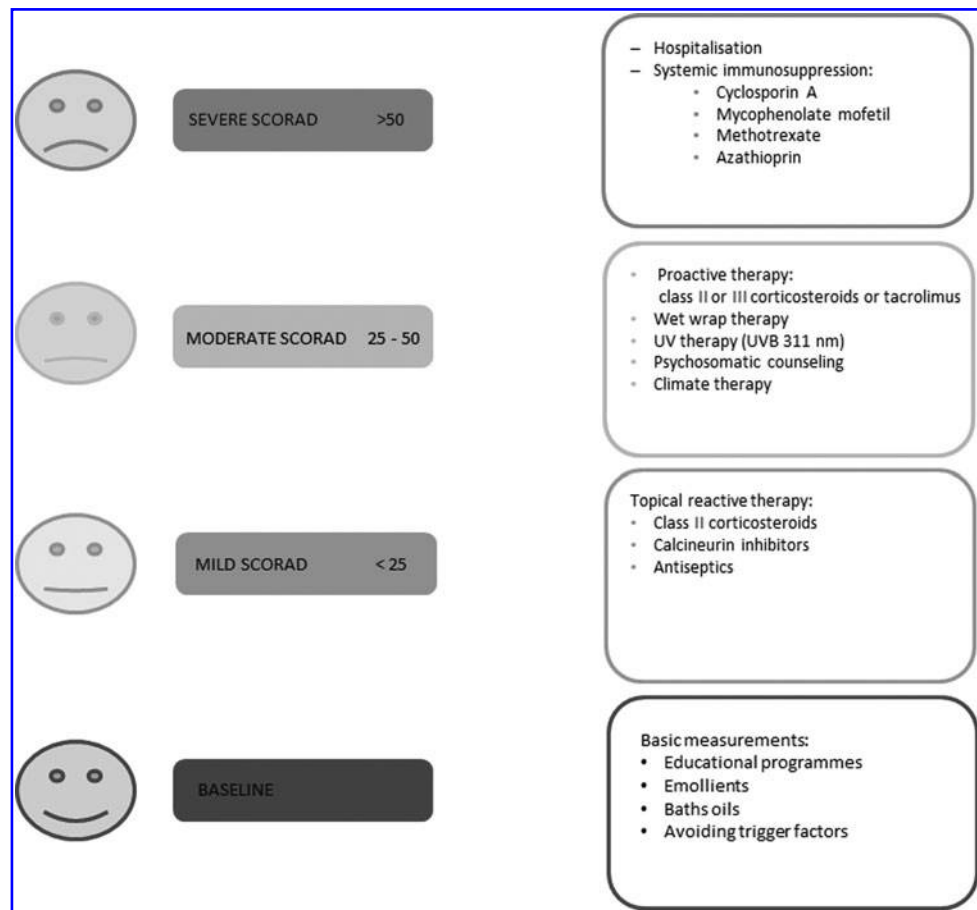
Multiple studies have shown that the use of emollients improves the skin of AD patients.^{9,10} These products reduce pruritus, improve the skin quality, and prolong the flare free time. The main function is to preserve the humidity of the skin.^{11,12} Humectants such as urea or glycerol will increase the water content of the outer skin layers. In the past years, a new category of emollients enriched with ceramides came on the market, which showed good results in comparison with a nonimproved ceramides formula.^{13,14} Emollients containing urea are not recommended for children less than the age of 2 years, and lower concentrations should be used in children <10 years of age.² Glycerol-containing emollients, in contrast, are

¹Department of Dermatology and Allergy, Ludwig-Maximilian University, Munich, Germany.

²Department of Dermatovenerology, Clinical Center of Serbia, Belgrade, Serbia.

³Department of Dermatology, King Abdulaziz University, Jeddah, Saudi Arabia.

FIG. 1. Treatment options for atopic dermatitis.



recommended even for preterm infants.² AD patients should use emollient formulations without fragrances or preservatives, as these substances are known allergens, causing contact dermatitis even in childhood.¹⁵

The wet wrap technique is a traditional method of topical treatment, which has been used for improving eczema and wounds, and is dating back to ancient Egypt.¹⁶ As children with acute oozing lesions may not tolerate a standard topical therapy, the wet wrap technique can be applied first until the oozing improves.¹⁰ The wet wraps can be performed either with emollients only or with diluted TCSs. The latter should be applied for a short period of time only, usually between 3 and 14 days.^{17,18} There are many modalities of preparing a wet wrap, which have been reviewed in detail by Oranje et al.¹⁶ The water used should be at body temperature, as cold water may provoke vasoconstriction and warm water may produce vasodilatation.^{19,20} A reapplication of the wet dressing may be necessary after ~30 min. The Rotterdam method of wet wraps encourages that the wet wrap should be rewetted every 2 h.¹⁶

Topical Antibacterial Therapy

Children suffering from AD have a tendency toward colonization *Staphylococcus aureus* and *Malassezia furfur* (*M. furfur*, also known as *Pitrosporon ovale*). Disseminated infection with the Herpes simplex virus and cutaneous infection with *S. aureus*, also known as impetiginization, are among the most relevant complications of AD in childhood.²¹

Topical antiseptic substances may be compounded into the emollients of AD patients to reduce their colonization with *S. aureus*, but the antiseptic substances must be chosen in a way that they are compatible with the emollient.¹² Triclosan, chlorhexidine, and octenidine are mostly used for these purposes.¹²

Topical antibiotic substances are generally not recommended for AD patients, as there is a potential for development of resistance and contact allergy.^{2,22} Topical tetracycline and topical aminoglycoside ointments are not recommended for AD treatment. Localized *S. aureus* infection especially of the eyelid region may be a good indication for topical treatment with fusidic acid.

Bathing of babies and children is clearly recommended, and should be done in warm but not hot water.¹⁰ Mild synthetic detergents should be used instead of traditional alkaline soap products.²⁰ The optimal frequency of bathing seems more a matter of personal preference, as there is no evidence-based recommendation for frequency available—every 2–4 days is a frequent recommendation.

Bathing in diluted solutions of potassium permanganate and sodium hypochlorite has been recommended to reduce the cutaneous colonization with *S. aureus*. There is good evidence that a 1:1,000 dilution of sodium hypochlorite, which equals the addition of 100 mL of normal household bleach to a bath tub filled with 100 L of tap water, will reduce the colonization with *S. aureus* and improve the treated body areas submerged in the diluted bleach bath.²³

Topical Anti-Inflammatory Therapy

Topical anti-inflammatory therapy is the mainstay of all flare intervention therapies of AD. TCSs and TCIs are the 2 relevant substance classes licensed for treatment of pediatric and adult AD. Localized occlusion—which may be achieved by saran wrap occlusion or wet wrap technology—will increase the absorption and therapeutic efficacy of TCSs and TCIs, but this will include both wanted and unwanted drug effects.

Topical corticosteroids

TCSs have been used for more than 60 years for their anti-inflammatory effect. A large diversity of formulations is available on the market.^{12,24} The choice of corticosteroid potency depends on the experience of the clinician. Topical therapy will usually start with a medium-potency TCS followed by a lower potency TCS, or may start with a low-potency TCS and is escalated only when no improvement is seen.^{12,25} Low-potency TCSs or highly diluted TCSs are usually preferred for infants.²⁶ The amount applied topically should follow the fingertip rule, with 1 fingertip unit being the equivalent of 0.5 g to be used on the area of an adult palm.²⁵ The amount of steroids recommended largely depends on the area and severity of the disease, which makes it difficult to recommend an exact amount to be used in children: in the acute phase of AD, infants less than 2 years may require an amount of 60–100 g ointment per week. In children less than 10 years of age, an amount of 250 g per week may be sufficient, whereas adolescents and young adults might require an amount of 300 g per week.^{27,28} As children have a higher degree of transcutaneous absorption, there is an increased risk of systemic side effects in this age group.²⁸ Side effects such as hyperglycemia, hypertension, glaucoma, adrenal suppression, and growth retardation may develop.²⁹ The newest generation of TCS formulations such as methylprednisolone aceponate, prednicarbate, fluticasone propionate, and mometasone furoate offers a better risk:benefit ratio with less systemic and local side effects.³⁰

All TCSs are less favored in the delicate body areas such as face, axillae, genitals, and eyelids because of their risk of skin atrophy, whereas TCIs have become the treatment of first choice for these delicate body areas.² Some patients and parents share their great concern regarding TCSs with their physicians, whereas others still have concerns but do not talk about it. This corticophobia may result in the discontinuation of TCS therapy, and determine a rebound of the AD.³¹

Topical calcineurin inhibitors

TCIs have good anti-inflammatory properties and good antipruritic effects, which largely result from their inhibition of proinflammatory cytokine production and mast cell degranulation.³² In contrast to TCSs, TCIs do not lead to skin atrophy.³² Tacrolimus ointment and pimecrolimus cream are approved for topical treatment of AD in children more than 2 years of age, but many clinical studies indicate that an off-label use in younger children is safe and effective.^{33,34} The efficacy of TCIs has been shown against placebo in short- and long-term clinical trials.²² The anti-inflammatory efficacy of 0.1% tacrolimus ointment is similar to that of intermediate strength TCSs, whereas the latter are more potent than 1.0%

pimecrolimus cream.¹² The most frequently reported side effect is a local warmth or burning sensation in the first days of application, which quickly improves if the TCSs are used twice daily. The safety profile of long-term use of tacrolimus and pimecrolimus in children has been demonstrated in a 2- and 5-year study, respectively.^{33,34}

Proactive Therapy

Proactive therapy is defined as a combination of pre-defined, long-term, low-dose anti-inflammatory treatment applied on the previously affected, usually relapsing skin areas together with daily emollient use on the rest of the body.³⁵ Proactive therapy of these “problem zones” of AD is usually performed twice weekly with TCSs or TCIs, and can be initiated only after all visible lesions have been cleared.³⁶ The additional application of emollients to the whole body should be performed at least once daily.³⁶ The efficacy of proactive therapy has been shown in 3-month studies for methylprednisolone aceponate and fluticasone propionate,^{37,38} and in 1 year studies for tacrolimus with adults and children.^{8,39} The barrier disruption of the skin is lower with proactive therapy than with continuous therapy, and is lower with TCIs than with TCSs.⁴⁰ The immunobiological background of proactive therapy lies in the fact that nonlesional skin of AD patients is not normal, but harbors a skin barrier defect, minimal inflammation, and an upregulation of the Immunoglobulin E (IgE) receptors on epidermal Langerhans cells.^{7,41,42} As the patient will actively address the disease according to his or her schedule and is not ruled in his or her action by a disease he or she cannot control, there is a behavioral aspect and concept behind proactive therapy.⁴³ There is clinical experience that proactive therapy using tacrolimus ointment and some medium-potency TCSs (Niedner classes II and III) works well in clinical reality.²

Systemic Immunosuppressive Drugs

The evidence for systemic treatment of AD in children and adolescents is largely derived from either adult studies or from study data generated for other diseases (Table 1). None of the suitable drugs for systemic treatment of AD in childhood is specifically licensed for this age group.² There are some publications on Cyclosporine (CyA) and systemic corticosteroids (SCS), which indicate their fast onset of efficacy. Methotrexate (MTX) and azathioprine (AZA) have mostly been used as long-term therapy for disease modification, and not for acute flare intervention.⁴⁴ The new substance class of Th2 blockers, such as dupilumab, is likely to substitute most of the immunosuppressive drugs nowadays used for severely affected children.⁴⁵

Systemic corticosteroids

Methylprednisolone is the most frequently used SCS, and has been advocated as being a safe and efficient treatment modality for the recalcitrant AD in the past century. Despite its wide use, there is a largely unfavorable risk:benefit ratio. Current guidelines and position articles prefer recommending other treatment options for long-term use in adults and children.^{2,22,46} The normal dose would be 0.5–1.0 mg/kg methylprednisolone given for about 1–2 weeks, followed by decreasing doses over a few weeks. An abrupt cessation of SCS frequently induces a rebound flare. Long-term use has a

TABLE 1. TREATMENT RECOMMENDATIONS AND DOSING GUIDELINE FOR SYSTEMIC IMMUNOSUPPRESSIVE AGENTS FOR ATOPIC DERMATITIS IN CHILDREN

Drug	Starting dose	Maintenance dose	Recommendations
Corticosteroids	0.5–1.0 mg/kg/day for 1–2 weeks	Reduce over a couple of weeks	Not really recommended, better be avoided. Use for acute and severe exacerbations only and only as short time therapy.
Cyclosporine A	(a) Start at 5 mg/kg/day (b) Start at 2.5 mg/kg/day	2.5–6 mg/kg/day (a) Reduce after 4 weeks according to response (b) Increase every 2 weeks in nonresponders	Effective therapy. Recommended for refractory AD.
Mycophenolate mofetil	30–50 mg/kg/day	Increase 500 mg every 2–4 weeks in nonresponders	Less effective therapy. May be considered as therapy for refractory AD.
Methotrexate	0.2–0.7 mg/kg/week test dose: 1.25–5 mg	0.2–0.7 mg/kg/week (a) Increase by 2.5–5 mg/week in nonresponders (b) Reduce with 2.5 mg/week	Effective therapy. Recommended for refractory AD. Requires folate supplementation.
Azathioprine	1–4 mg/kg/day	1–4 mg/kg/day	Effective therapy. Recommended for refractory AD.

AD, atopic dermatitis.

significant risk for adrenal suppression.^{46,47} Most of the clinicians are well aware of the side effects brought by an SCS therapy. The most dramatic side effects in the pediatric population are hypertension, weight gain, decreased bone density, decreased growth, and adrenal suppression.⁴⁸

Cyclosporine A

CyA is a calcineurin inhibitor interfering with the proinflammatory cytokine production dependent on the nuclear factor of activated T cells. T cells, mast cells, and dendritic cells are known cellular targets of CyA.⁴⁹ CyA is approved for treatment of AD in adults in most European countries, whereas treatment of children is an off label use. There is quite large experience with using CyA in children. Safety and efficacy in children are at least as good as in adults.^{50–52} Actually, children tolerate CyA quite well and show little or no renal side effects. Although CyA may lead to nephrotoxicity and hypertension in long-term use, continuous low-dose CyA use over a 1-year period showed good safety results.⁵³ The risk of hypertension and pseudotumor cerebri must be considered.⁵⁴ The pediatric CyA dosing is similar to adult CyA dosing, and can range from 3 to 5 or even 6 mg/kg CyA per day.^{2,22,46,47} Therapy is usually started with a dose of 5 mg/kg per day divided into two 2.5 mg doses, and can be reduced after 4 weeks according to clinical response.⁵³ Starting with a low-dose therapy of 2.5 mg/kg with progressive augmentation every 2 weeks for nonresponders is also possible, but the drug survival of this approach is not as good.^{55–57} In summary, CyA is in most cases the preferred drug for short-term intervention in children with severe AD.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) affects the purine biosynthesis pathway of human cells and, therefore, blocks selectively the proliferation of B and T lymphocytes. Owing to its high specificity for lymphocytes, MMF has a good safety profile in adults and children.^{2,58} The standard dose for adult patients is 2 g per day divided into 2 oral doses of 1 g. MMF has not been approved for the treatment of AD in children yet, but it is a recognized safe off-label therapy for

recalcitrant AD in children.^{47,59} The pediatric dose may range between 30 and 50 mg/kg per day.^{2,47} No substantial side effects such as leucopenia, anemia, thrombocytopenia, or elevated liver parameters were identified in a small cohort of 14 children on MMF.⁵⁹ The most frequently observed side effects are transient gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal discomfort. The overall clinical efficacy of MMF seems lower than that of CyA, MTX, or AZA, but its tolerability and safety profile seem to be excellent in children.

Methotrexate

The purine antagonist MTX interferes with purine and pyrimidine synthesis, thereby reducing T cell proliferation. Low-dose MTX therapy has shown good results in treatment of adult patients with recalcitrant AD. MTX can be used with confidence in children, as its effectiveness and safety profile for children have been proven in multiple studies.⁶⁰ MTX was administered in 25 children and showed 76% clearance of the skin lesions.⁶¹ Mild gastrointestinal side effects were predominant and no substantial side effects reported. The pediatric dose ranges between 0.2 and 0.7 mg/kg given once weekly.^{2,47} Each MTX cycle must be pursued by a folic acid substitution.² Therapeutic response can be expected after 3–8 weeks, which is slow compared with that of CyA but similar to that of AZA and MMF.⁶² The long-term drug survival of MTX is better than that of CyA, making it a good option for long-term treatment of children with severe AD.⁶³

Azathioprine

The purine analogue AZA inhibits DNA production and targets highly proliferative cells such as B cells and T cells. The pediatric dose ranges between 1 and 4 mg/kg per day. Thiopurine methyltransferase (TPMT) levels should be determined before starting the drug,^{47,64,65} as low TPMT levels are associated with higher treatment efficacy, as well as increased risk of myelosuppression.⁶⁶ Therefore, the initial dose should be adjusted according to the TPMT results. Determination of TPMT levels should be repeated in nonresponding patients.^{47,67} It takes 8–12 weeks until the

maximal clinical efficiency of AZA is reached.^{2,67} The side effects in the pediatric population are mostly associated with mild gastrointestinal complaints, elevated hepatic transaminases, and cutaneous viral infections.

Biologics

A number of traditional biologics mostly licensed for psoriasis or chronic urticaria have also been tried for AD, but the results were all discouraging.² Omalizumab (OMB) is a humanized monoclonal antibody that binds IgE. OMB improved some cases of AD, but a randomized pediatric trial versus placebo failed to show significant improvement.⁶⁸ Other traditional biologics such as mepolizumab (anti-IL5), etanercept (anti-TNF-alpha), tocilizumab (anti-IL6), and rituximab (anti-CD20) have also failed to show a significant improvement, or presented severe side effects when studied in adults.^{45,69}

Dupilumab is an inhibitory monoclonal antibody binding the common alpha chain of the IL4 and IL13 receptor, thus selectively targeting the Th2 pathway of inflammation. Phase 2b and phase 3 studies have shown that dupilumab is safe and effective for moderate-to-severe AD in adults.^{45,69} Skin infections in the dupilumab group were less frequent than in the placebo group.⁶⁹ A pediatric phase 3 study with dupilumab is currently underway, but results have not been published.

Nemolizumab is an inhibitory monoclonal antibody binding the IL31 receptor, thus inhibiting a highly important pathway of itch in AD.⁷⁰ Results of an adult phase 2 study show good efficacy regarding the symptoms itch and sleep disturbance.

Therapeutic Patient Education

Therapeutic patient education of children, adolescents, and parents of children suffering from AD is an unbeatable safe and extremely effective way of intervention for AD.⁷¹ Interdisciplinary group education given by physicians, nurses, psychologists, and nutrition specialists will not only improve patient knowledge about the impact of food, textiles, immunology, stress, or basic therapy on their AD but also improve signs and symptoms of AD and improve quality of life.^{71,72} Interaction between participants is an important aspect of the intervention, which is also useful in the adult age.⁷³ The worldwide experience with these programs is excellent.^{74,75} All current guidelines recommend participation in one of these therapeutic patient education programs.^{2,22,46,73}

Conclusion

Management of acute flares in pediatric AD patients is possible in most situations if certain standards of care are followed. These have been reviewed and assessed in multiple recent position articles and guidelines, such as the European Task Force of Atopic Dermatitis position article, the European Dermatology Forum guideline, and the American Academy of Dermatology guideline.^{2,46,73} The majority of moderate and severe AD patients can be maintained in a flare-free state using the proactive approach^{36,76}; there is an unmet need for an effective disease-modifying drug lacking immunosuppressive, hepatotoxic, and nephrotoxic side effects. The new functional substance class of Th2-blocking biologics, such as dupilumab or tralokinumab, as well as the new biologics blocking the IL31 pathway, is expected to enhance the therapeutic options for pediatric AD patients within the near future.

Author Disclosure Statement

No competing financial interests exist.

References

1. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014; 71:116–132.
2. Wollenberg A, Oranje A, Deleuran M, 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; 30:729–747.
3. Arkwright PD, Motala C, Subramanian H, et al. Management of difficult-to-treat atopic dermatitis. *J Allergy Clin Immunol Pract* 2013; 1:142–151.
4. European Task Force on Atopic Dermatitis. Severity scoring of atopic dermatitis: the SCORAD Index. *Dermatology* (Basel, Switzerland) 1993; 186:23–31.
5. Stalder JF, Barbarot S, Wollenberg A, et al. Patient-oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011; 66:1114–1121.
6. Kunz B, Oranje AP, Labrèze L, Stalder JF, Ring J, Taïeb A. Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on Atopic Dermatitis. *Dermatology* 1997; 195:10–19.
7. Proksch E, Folster-Holst R, Jensen JM. Skin barrier function, epidermal proliferation and differentiation in eczema. *J Dermatol Sci* 2006; 43:159–169.
8. Wollenberg A, Reitamo S, Girolomoni G, et al. Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy* 2008; 63:742–750.
9. Breternitz M, Kowatzki D, Langenauer M, Elsner P, Fluhr JW. Placebo-controlled, double-blind, randomized, prospective study of a glycerol-based emollient on eczematous skin in atopic dermatitis: biophysical and clinical evaluation. *Skin Pharmacol Physiol* 2008; 21:39–45.
10. Gelmetti C, Wollenberg A. Atopic dermatitis—all you can do from the outside. *Br J Dermatol* 2014; 170 Suppl 1:19–24.
11. Tamura M, Kawasaki H, Masunaga T, Ebihara T. Equivalence evaluation of moisturizers in atopic dermatitis patients. *J Cosm Sci* 2015; 66:295–303.
12. Wollenberg A, Schnopp C. Evolution of conventional therapy in atopic dermatitis. *Immunol Allergy Clin N Am* 2010; 30:351–368.
13. Hon KL, Tsang YC, Pong NH, et al. Patient acceptability, efficacy, and skin biophysiology of a cream and cleanser containing lipid complex with shea butter extract versus a ceramide product for eczema. *Hong Kong Med J* 2015; 21:417–425.
14. Silverberg JI, Nelson DB, Yosipovitch G. Addressing treatment challenges in atopic dermatitis with novel topical therapies. *J Dermatol Treat* 2016; [Epub ahead of print], DOI: 10.1080/09546634.2016.1174765.
15. 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; 29:1071–1081.
16. Oranje AP, Devillers AC, Kunz B, et al. Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert panel's opinion and review of the literature. *J Eur Acad Dermatol Venereol* 2006; 20:1277–1286.

17. Devillers AC, Oranje AP. Wet-wrap treatment in children with atopic dermatitis: a practical guideline. *Pediatr Dermatol* 2012; 29:24–27.
18. Janmohamed SR, Oranje AP, Devillers AC, et al. The proactive wet-wrap method with diluted corticosteroids versus emollients in children with atopic dermatitis: a prospective, randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol* 2014; 70:1076–1082.
19. Kohn LL, Kang Y, Antaya RJ. A randomized, controlled trial comparing topical steroid application to wet versus dry skin in children with atopic dermatitis (AD). *J Am Acad Dermatol* 2016; 75:306–311.
20. Blume-Peytavi U, Cork MJ, Faergemann J, Szczapa J, Vanaclocha F, Gelmetti C. Bathing and cleansing in newborns from day 1 to first year of life: recommendations from a European round table meeting. *J Eur Acad Dermatol Venereol* 2009; 23:751–759.
21. Wollenberg A, Wetzel S, Burgdorf WH, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003; 112: 667–674.
22. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part I. *J Eur Acad Dermatol Venereol* 2012; 26:1045–1060.
23. Huang JT, Abrams M, Tloughan B, Rademaker A, Paller AS. Treatment of *Staphylococcus aureus* colonization in atopic dermatitis decreases disease severity. *Pediatrics* 2009; 123:e808–e814.
24. Hepburn DJ, Aeling JL, Weston WL. A reappraisal of topical steroid potency. *Pediatr Dermatol* 1996; 13:239–245.
25. Eichenfield LF, Boguniewicz M, Simpson EL, et al. Translating atopic dermatitis management guidelines into practice for primary care providers. *Pediatrics* 2015; 136:554–565.
26. Cheigh NH. Managing a common disorder in children: Atopic dermatitis. *J Pediatr Health Care* 2003; 17:84–88; quiz 89–90.
27. Bewley A. Expert consensus: time for a change in the way we advise our patients to use topical corticosteroids. *Br J Dermatol* 2008; 158:917–920.
28. Long CC, Mills CM, Finlay AY. A practical guide to topical therapy in children. *Br J Dermatol* 1998; 138: 293–296.
29. Kristmundsdottir F, David TJ. Growth impairment in children with atopic eczema. *J R Soc Med* 1987; 80:9–12.
30. Korting HC, Schollmann C. Topical fluticasone propionate: intervention and maintenance treatment options of atopic dermatitis based on a high therapeutic index. *J Eur Acad Dermatol Venereol* 2012; 26:133–140.
31. Moret L, Anthoine E, Aubert-Wastiaux H, et al. TOPI-COP(c): a new scale evaluating topical corticosteroid phobia among atopic dermatitis outpatients and their parents. *PLoS One* 2013; 8:e76493.
32. Bornhövd E, Burgdorf WHC, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. *J Am Acad Dermatol* 2001; 45:736–743.
33. Mandelin JM, Rubins A, Remitz A, et al. Long-term efficacy and tolerability of tacrolimus 0.03% ointment in infants: a two-year open-label study. *Int J Dermatol* 2012; 51:104–110.
34. Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics* 2015; 135:597–606.
35. Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis—an emerging concept. *Allergy* 2009; 64:276–278.
36. Wollenberg A, Ehmann LM. Long term treatment concepts and proactive therapy for atopic eczema. *Ann Dermatol* 2012; 24:253–260.
37. Berth-Jones J, Damstra RJ, Golsch S, et al. Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *Br Med J* 2003; 326:1367.
38. Peserico A, Stadler G, Sebastian M, Fernandez RS, Vick K, Bieber T. Reduction of relapses of atopic dermatitis with methylprednisolone aceponate cream twice weekly in addition to maintenance treatment with emollient: a multicentre, randomized, double-blind, controlled study. *Br J Dermatol* 2008; 158:801–807.
39. Thaci D, Reitamo S, Gonzalez Ensenat MA, et al. Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; 159: 1348–1356.
40. Chittock J, Brown K, Cork MJ, Danby SG. Comparing the effect of a twice-weekly tacrolimus and betamethasone valerate dose on the subclinical epidermal barrier defect in atopic dermatitis. *Acta Derm Venereol* 2015; 95:653–658.
41. Mihm MC, Soter NA, Dvorak HF, Austen KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976; 67:305–312.
42. Wollenberg A, Wen S, Bieber T. Phenotyping of epidermal dendritic cells: clinical applications of a flow cytometric micromethod. *Cytometry* 1999; 37:147–155.
43. Wollenberg A, Frank R, Kroth J, Ruzicka T. Proactive therapy of atopic eczema—an evidence-based concept with a behavioral background. *J Dtsch Dermatol Ges* 2009; 7: 117–121.
44. Tsakok T, Flohr C. Methotrexate vs. ciclosporin in the treatment of severe atopic dermatitis in children: a critical appraisal. *Br J Dermatol* 2014; 170:496–498; discussion 98–99.
45. 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; [Epub ahead of print], DOI: 10.1056/NEJMoa1610020.
46. Ring J, Alomar A, Bieber T, et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II. *J Eur Acad Dermatol Venereol* 2012; 26:1176–1193.
47. Sidbury R, Davis DM, Cohen DE, 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; 71:327–349.
48. van Velsen SG, Knol MJ, van Eijk RL, et al. Bone mineral density in children with moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2010; 63:824–831.
49. Bornhövd EC, Burgdorf WHC, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. *Curr Opin Investig Drugs* 2002; 3: 708–712.
50. Bulbul Baskan E, Yazici S, Tunalı S, Saricaoglu H. Clinical experience with systemic cyclosporine A treatment in severe childhood psoriasis. *J Dermatol Treat* 2016; 27:328–331.
51. Sibbald C, Pope E, Ho N, Weinstein M. Retrospective review of relapse after systemic cyclosporine in children with atopic dermatitis. *Pediatr Dermatol* 2015; 32:36–40.
52. Ricci G, Dondi A, Patrizi A, Masi M. Systemic therapy of atopic dermatitis in children. *Drugs* 2009; 69:297–306.
53. Harper JI, Ahmed I, Barclay G, et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy. *Br J Dermatol* 2000; 142:52–58.

54. Blasco Morente G, Tercedor Sanchez J, Garrido Colmenero C, Martinez Garcia E, Molina-Carballo A. Pseudotumor cerebri associated with cyclosporine use in severe atopic dermatitis. *Pediatr Dermatol* 2015; 32:237–239.
55. Bunikowski R, Staab D, Kussebi F, et al. Low-dose cyclosporin A microemulsion in children with severe atopic dermatitis: clinical and immunological effects. *Pediatr Allergy Immunol* 2001; 12:216–223.
56. van der Schaft J, Politiek K, van den Reek JM, et al. Drug survival for ciclosporin A in a long-term daily practice cohort of adult patients with atopic dermatitis. *Br J Dermatol* 2015; 172:1621–1627.
57. van der Schaft J, van Zuilen AD, Deinum J, Bruijnzeel-Koomen CA, de Bruin-Weller MS. Serum creatinine levels during and after long-term treatment with cyclosporin A in patients with severe atopic dermatitis. *Acta Derm Venereol* 2015; 95:963–967.
58. Haeck IM, Knol MJ, Ten Berge O, van Velsen SG, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Enteric-coated mycophenolate sodium versus cyclosporin A as long-term treatment in adult patients with severe atopic dermatitis: a randomized controlled trial. *J Am Acad Dermatol* 2011; 64:1074–1084.
59. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; 157:127–132.
60. El-Khalawany MA, Hassan H, Shaaban D, Ghonaim N, Eassa B. Methotrexate versus cyclosporine in the treatment of severe atopic dermatitis in children: a multicenter experience from Egypt. *Eur J Pediatr* 2013; 172:351–356.
61. Roberts H, Orchard D. Methotrexate is a safe and effective treatment for paediatric discoid (nummular) eczema: a case series of 25 children. *Australas J Dermatol* 2010; 51: 128–130.
62. Irvine AD. Commentary: methotrexate and ciclosporin in the treatment of severe eczema in children. *Br J Dermatol* 2014; 170:499–500.
63. Politiek K, Schaft JV, Coenraads PJ, de Bruin-Weller MS, Schuttelaar ML. Drug survival for methotrexate in a daily practice cohort of adult patients with severe atopic dermatitis. *Br J Dermatol* 2016; 174:201–203.
64. Caufield M, Tom WL. Oral azathioprine for recalcitrant pediatric atopic dermatitis: clinical response and thiopurine monitoring. *J Am Acad Dermatol* 2013; 68:29–35.
65. Werfel T, Heratizadeh A, Aberer W, et al. S2k guideline on diagnosis and treatment of atopic dermatitis—short version. *J Dtsch Dermatol Ges* 2016; 14:92–105.
66. Schram ME, Roekevisch E, Leeftang MM, Bos JD, Schmitt J, Spuls PI. A randomized trial of methotrexate versus azathioprine for severe atopic eczema. *J Allergy Clin Immunol* 2011; 128:353–359.
67. Fuggle NR, Bragoli W, Mahto A, Glover M, Martinez AE, Kinsler VA. The adverse effect profile of oral azathioprine in pediatric atopic dermatitis, and recommendations for monitoring. *J Am Acad Dermatol* 2015; 72:108–114.
68. Iyengar SR, Hoyte EG, Loza A, et al. Immunologic effects of omalizumab in children with severe refractory atopic dermatitis: a randomized, placebo-controlled clinical trial. *Int Arch Allergy Immunol* 2013; 162:89–93.
69. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; 371:130–139.
70. Nemoto O, Furue M, Nakagawa H, et al. The first trial of CIM331, a humanized antihuman interleukin-31 receptor A antibody, in healthy volunteers and patients with atopic dermatitis to evaluate safety, tolerability and pharmacokinetics of a single dose in a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2016; 174: 296–304.
71. Staab D, Diepgen TL, Fartasch M, et al. Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *Br Med J* 2006; 332:933–938.
72. Kupfer J, Gielert U, Diepgen TL, et al. Structured education program improves the coping with atopic dermatitis in children and their parents—a multicenter, randomized controlled trial. *J Psychosom Res* 2010; 68:353–358.
73. Sidbury R, Tom WL, Bergman JN, et al. Guidelines of care for the management of atopic dermatitis: section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol* 2014; 71: 1218–1233.
74. Barbarot S, Bernier C, Deleuran M, et al. Therapeutic patient education in children with atopic dermatitis: position paper on objectives and recommendations. *Pediatr Dermatol* 2013; 30:199–206.
75. Stalder JF, Bernier C, Ball A, et al. Therapeutic patient education in atopic dermatitis: worldwide experiences. *Pediatr Dermatol* 2013; 30:329–334.
76. Roekevisch E, Spuls PI, Kuester D, Limpens J, Schmitt J. Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: a systematic review. *J Allergy Clin Immunol* 2014; 133:429–438.

Address correspondence to:
 Andreas Wollenberg, MD
 Dept. of Dermatology and Allergy
 Ludwig Maximilian University
 Frauenlobstr. 9–11
 80337 Munich
 Germany

E-mail: wollenberg@lrz.uni-muenchen.de

Received for publication October 24, 2016; accepted after revision November 17, 2016.