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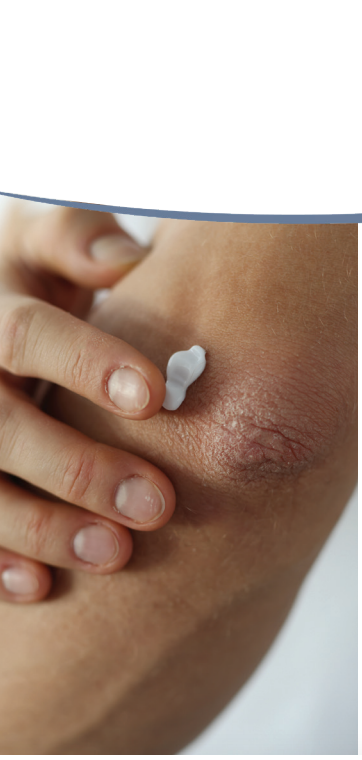
UPDATES ON DERMATOLOGY

ATOPY



ECOBIOLOGY AT THE SERVICE OF DERMATOLOGY

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EDITO

Stéphane FAUVERGHE
NAOS International Medical Relations Director

Dear All,

I am very pleased to present you the 1st edition of Bioderma Updates Series dedicated to Atopy.

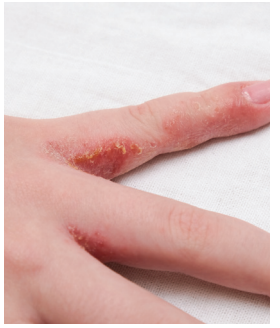
Since 2020, BIODERMA is regularly organizing International e-symposia dedicated to Dermatology, for dermatologists and all health care professionals interested in Dermatology, with always high-level updates on skin disorders presented by renowned experts in their field.

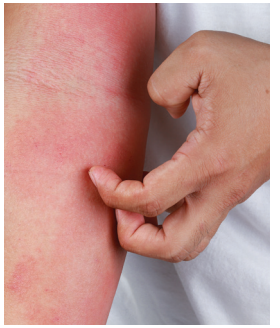
*In this 1st publication, you will find the summary of the recent e-symposium on **Atopy : Highlights & New Insights**, with Prof. Carsten FLOHR from UK, Prof. Laurent MISERY from France and Dr. Sandy SKOTNICKI from Canada as speakers.*

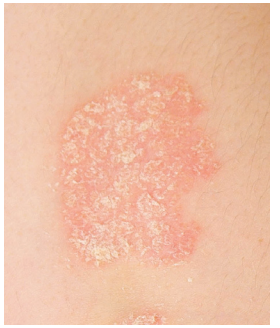
During this e-symposium, Carsten FLOHR presented new data on systemic treatments for children suffering from atopy, Laurent MISERY delivered an update on itching and finally Sandy SKOTNICKI presented the role of skin care in the management of atopy & its impact on the skin barrier.

I wish you all an enjoyable, enriching and interesting reading.

SUMMARY







SPEAKERS'S SHORT BIOGRAPHIES

Carsten FLOHR

United Kingdom

Professor Carsten FLOHR holds the Chair in Dermatology and Population Health Science at St John's Institute of Dermatology, King's College London, where he directs the Unit for Population-Based Dermatology Research.

He studied at Cambridge and Oxford Universities and then trained in both Paediatrics and Dermatology.

Carsten FLOHR was the first UK National Institute for Health Research (NIHR) Clinician Scientist in Dermatology (2009-2014) and the only dermatologist awarded a Career Development Fellowship from the NIHR (2014-2019).

He has a particular interest in novel methods of atopic dermatitis (AD) prevention (early life risk factors) and therapeutics, especially in severe AD.

He is Chief Investigator of the UK-Irish TREatment of severe eczema in children Trial (TREAT), which compares cyclosporine with methotrexate in children with recalcitrant atopic eczema. He is also Chief Investigator of the Softened water for eczema prevention trial (SOFTER) and the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR), as well as the EU-funded BIOMAP and Trans-Foods consortia.

Prof. FLOHR is a Founding Director of the International Eczema Council and Past President of the British Society of Paediatric Dermatology, as well as an Honorary Member of the Société Française de Dermatologie.

He is also Founding Editor of the Evidence-Based Dermatology Section of the British Journal of Dermatology and the Clinical Trials Editor of the F1000 Atopic Dermatitis Section.

Laurent MISERY

France

After studies and his first professional years in Lyon and Saint Etienne, Laurent MISERY became professor of Dermatology at the University of Brest.

He is now head of the department of Dermatology at the University Hospital of Brest.

Laurent MISERY founded and is the director of the Laboratory on Interactions Neurons-Keratinocytes (LINK) and the French Expert Centre on Itch. His team is dedicated to translational research on itch, from fundamental (biological and physiological) to pathophysiological, clinical, psychological and therapeutic aspects.

He is especially interested in the relationship between skin and the nervous system, from the biological point of view (co-cultures between skin cells and neurons) to the clinical (pruritus, sensitive skin) or psychological points of view.

Prof. MISERY is chairman of the EADV task force of psychodermatology.

His research interest is : sensitive skin; skin irritation; irritant; sensitivity; skincare products.

He was distinguished with the Herman Musaph Award in 2017.

Sandy SKOTNICKI

Canada

Dr. Sandy SKOTNICKI is the founding director of the Bay Dermatology Centre and is Assistant Professor at the University of Toronto, Department of Medicine in the Divisions of Dermatology and Occupational and Environmental Health. Dr. SKOTNICKI started the Bay Dermatology Centre in 2006 in an effort to provide a full-service Dermatology centre that focuses on the patient, not procedures.

She is a Diplomat of the American Board of Dermatology, and a member of the Canadian Medical Association, Canadian Dermatology Association, American Dermatology Association and American Contact Dermatitis Society.

Dr. SKOTNICKI is a consultant Dermatologist at St. Michael's Hospital in Toronto and is an expert in Allergic Skin Disease. She is also a consultant for the Workplace Safety Insurance Board.

Active in research and education, Dr. SKOTNICKI has been teaching University of Toronto Dermatology, Allergy and Family Medicine residents at her St. Michael's Hospital clinic since 1999. She is also a member of the Centre for Research Expertise in Occupational Disease & has published numerous articles on different aspects of Allergic Skin Disease.

Widely regarded as the "go to" Dermatologist in Canada for ingredient reactions and safety, she regularly provides commentary and contributes to medical journals, media outlets and speaks on reactions to chemicals in the skin-care industry.

COMPLEX PEDIATRIC ATOPIC DERMATITIS: A SPOTLIGHT ON SYSTEMIC THERAPIES

CARSTEN FLOHR

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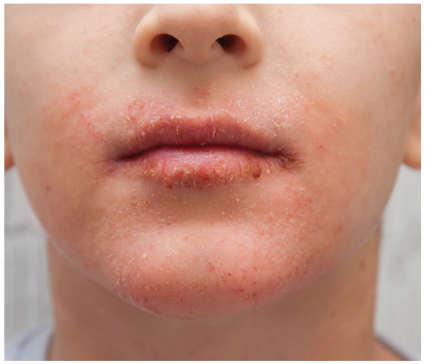
Guy's & St Thomas' NHS Foundation Trust, King's College, *London, UK*



While nowadays the therapeutic revolution in systemic therapies in atopic dermatitis (AD) is impressive, it still mainly focuses on adults, while pediatric trials are commonly performed once studies in adults have been completed. With several novel systemic treatments having been marketed, new therapeutic options are more and more frequently available for the pediatric population.

This article provides some information about conventional as well as novel treatment options in AD, along with an explanation of their targets within the complex inflammatory pathways in AD. Moreover, it provides three cases of severe pediatric eczema and how these cases were managed.

Based on the enhanced understanding of the immunological pathways in AD, a large number of therapeutic targets have now been identified. These include cytokines, such as Interleukin (IL)-33 targeted by Lebrikizumab, the cytokine thymic stromal lymphopoietin (TSLP) targeted by Tralokinumab and the Th2 signaling pathway targeted by Dupilumab.[1-4]

Dupilumab, the most frequently used biologic, is a human monoclonal antibody directed against the IL-4Rα subunit of the IL-4 and IL-13 receptors.[5, 6] A clinical study with Dupilumab conducted in children aged between 6 and 11 years provided similar results to those in adolescents with uncontrolled moderate to severe AD.[7, 8] It was overall well tolerated, even though cases of eosinophilia and conjunctivitis were reported.[9, 10] Conversely, blocking IL-5, IL-22 and IL-23 signaling has not yielded much promise for AD and pediatric study results for Nemolizumab, targeting the itch-mediating cytokine IL-31 are lacking.[11] Selective JAK inhibitors, which are broader in their anti-inflammatory effect, are eagerly awaited, while data on Omalizumab in pediatric AD has not shown improvement at the level of a minimal clinically important difference (MCID) in disease severity.[12]

To date, Cyclosporine A remains the only conventional systemic that is licensed in AD patients aged above 16 years, one of main reasons why it is still widely prescribed.[19]

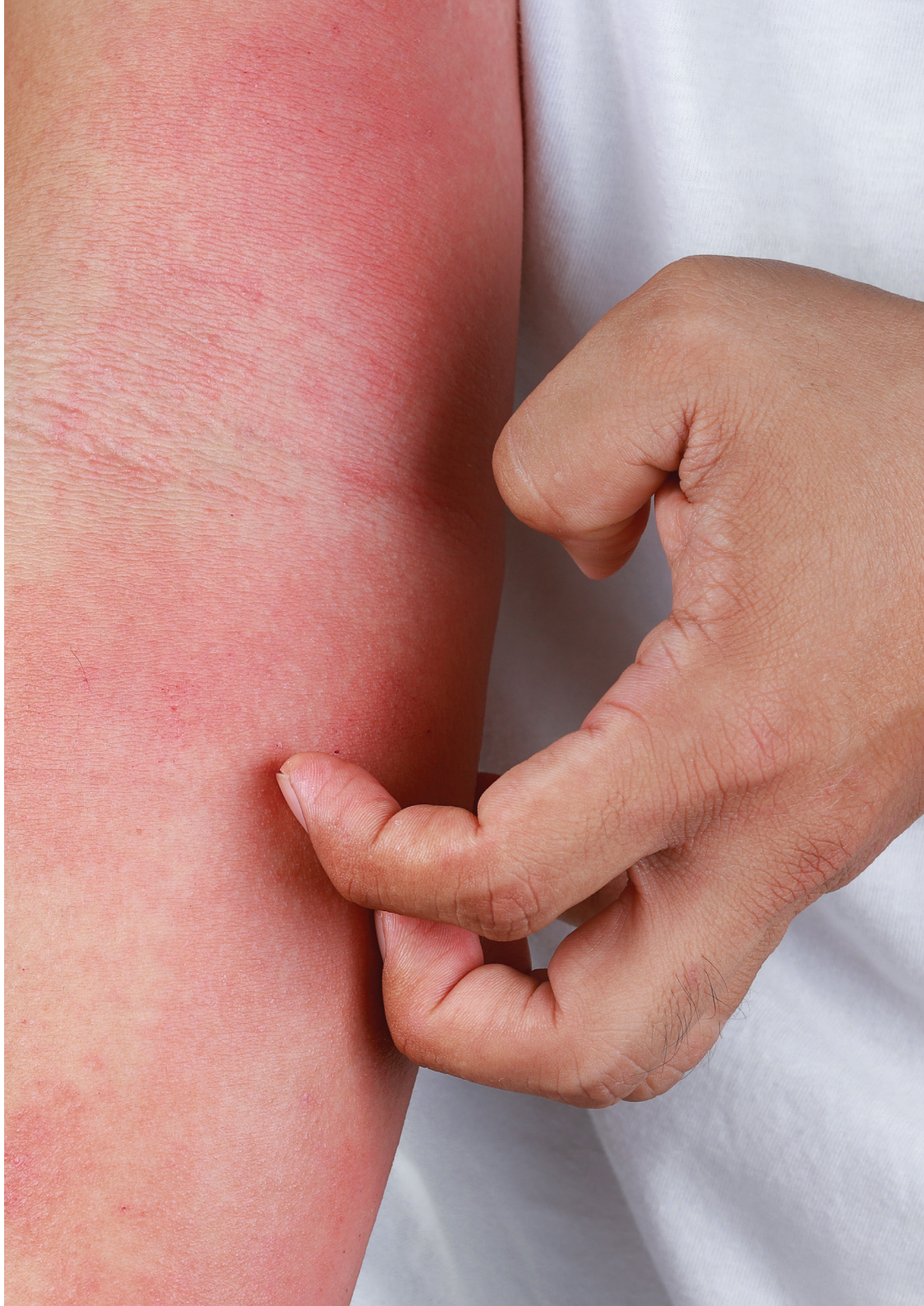
Overall, there is only a small amount of data about the use of systemic medications in pediatric AD populations available, mainly case series and case-control studies. Where pediatric data are available from clinical trials, the assessed treatments are often not commonly used, if at all. Moreover, it is frequent that pediatric patient data is not separately reported in clinical studies.[19-26]

Currently, there is only one published paediatric AD clinical trial that has assessed the efficacy of Methotrexate and Cyclosporine A, suggesting that both treatments work equally well with a SCORAD reduction just under 50 % after 24 weeks. Both drugs were well tolerated.[27] However, the study was small (20 participants per study arm) and therefore statistically underpowered, and the agents under-dosed; 2.5 mg/kg/day for Cyclosporin A and a fixed dose of 7.5 mg per week for Methotrexate.

Conversely, in the UK and many other settings where licensing considerations are not important, Methotrexate has emerged as the 1st line conventional systemic for AD in most departments. However, as for all immunosuppressive drugs, it bears safety concerns and long-term safety data from AD cohorts are currently missing.[28] Interestingly, latest research indicates that Methotrexate works as a selective Janus kinase inhibitor.[29]

Known side effects of Methotrexate include nausea, liver disturbance, and, rarely, bone marrow suppression. However, it is generally considered safe during long-term administration for paediatric patients. Its relatively slow onset of action and, while there is no clinical evidence, it is supposed to have the potential to induce long-term remission.[30]

Therefore, treating severe AD should consist of much more than starting a systemic medication. AD is a multifactorial and complex disease, driven by the vicious itch-scratch cycle. Itching can cause profound sleep disruption and many patients suffer from psychological and psychiatric comorbidities.[31] Scratching frequently causes skin infections, contributing to disease flares and chronicity, and many patients also report concomitant food and respiratory allergies that feed into the disease process.[32] For this reason, treating severe AD should always be a team approach. Ideally, a multidisciplinary team that includes pediatric dermatologists, clinical nurse specialists, pediatric allergists and clinical psychologists, pediatric respiratory medicine, and , where available, a research team to provide access to new therapeutics all help to treat severe pediatric AD in a holistic way.



In the following paragraphs, three cases of children with severe AD who were treated in our clinic are presented.

CASE N°1

The 1st case reported the treatment journey of an 8 year-old boy with severe AD since early life; who also suffered from hay fever and asthma. He was dependent on potent topical steroids and oral prednisolone, suffered from recurrent infective exacerbations and had several hospital admissions for this. Moreover, due to frequent safety blood taking, he had developed a profound needle phobia. His AD worsened with phototherapy and he developed high blood pressure and renal impairment on Cyclosporin A. Despite adequate metabolite levels, he was non-respondent to Azathioprine, Methotrexate and Mycophenolate Moletil. He then successfully received Dupilumab in compassionate use, with a remarkable treatment outcome, even after 10 months of continued use.

CASE N°2

The 2nd case concerned a 10-year old girl in whom all conventional treatments had failed. She received Mycophenolate mofetil (after having been unsuccessfully treated with Cyclospirin A and Methotrexate) as well as prophylactic oral antibiotics for her recurrent bacterial skin infections, with an insufficient treatment outcome. She then received Dupilumab at 200mg, leading to a cleared AD after six weeks. However, after about four months into Dupilumab therapy she developed yet another severe infection-driven flare, and her AD did not settle down sufficiently, once the skin infection had been adequately treated. Methotrexate was subsequently added in to the Dupilumab, but this did not result in adequate disease control either. She has now been switched to Abrocitinib with a good treatment effect.

Unfortunately, she has already had several episodes of herpes simplex infections since starting the medication, requiring Valaciclovir prophylaxis.

CASE N°3

The 3rd case concerned a 10-year old girl with a lifelong, severe AD, brittle asthma, severe hay-fever and many allergies, and who failed on all conventional treatments. She could not participate in any clinical trial, for instance with Baricitinib, as she required oral Prednisolone and hospital admission when undergoing the washout period.

Based on the above described evidence and on the experiences observed in his clinic, Carsten FLOHR considers that further novel treatments are urgently needed to treat pediatric AD. Moreover, head-to-head studies between conventional and novel treatments, as well as between conventional and between novel treatments, should be performed to directly assess the clinical efficacy of the different systemic AD treatments, thus allowing for a ranking in efficacy. In the meantime, network meta-analyses allow multiple comparisons of treatments in a unified analysis, including not only direct head-to-head study data but also indirect treatment comparisons from placebo-controlled trials.[33, 34] An update of Drucker *et al.* on this issue has been published in 2020.[35]

Moreover, treatment registries will be helpful vehicles to assess the long-term treatment effectiveness and safety of both novel and conventional systemic medications, also because many patients are excluded from participation in clinical trials due to rather strict inclusion criteria.

To this end, the UK-Irish A-STAR and other national AD systemic treatment registries provide 'real world' data on the more long-term treatment effectiveness and safety for systemic atopic eczema medication, comparing conventional and novel agents. Some registries also include a health economic assessment and a bioresource for molecular and stratification studies.

KEY MESSAGES

- Conventional systemic treatments remain the standard first line treatments for severe pediatric AD in most countries
- Of those, methotrexate (0.4 mg/kg/week) is now increasingly used
- Cyclosporin A at 4-5 mg/kg/day may be indicated for a faster onset of action, but data from an adequately powered RCT comparing Cyclosporin A with Methotrexate is currently lacking
- Dupilumab is now licensed for children from 6 years of age
- JAK inhibitors (Abrocitinib and Upadacitinib) are promising new therapies, even in those patients who failed treatment with Dupilumab
- Treatment registries to assess the long-term treatment effectiveness and safety are needed, as well as more head-to-head (rather than placebo-controlled)
- Network meta-analyses allow us to compare the efficacy of the different conventional and novel therapies, even if most of the evidence comes from placebo-controlled trials

REFERENCES

1. Guttman-Yassky E, Blauvelt A, Eichenfield LF, Paller AS, Armstrong AW, Drew J, *et al. Efficacy and Safety of Lebrikizumab, a High-Affinity Interleukin 13 Inhibitor, in Adults With Moderate to Severe Atopic Dermatitis: A Phase 2b Randomized Clinical Trial.* JAMA Dermatol. 2020;156(4):411-20.

2. Wollenberg A, Blauvelt A, Guttman-Yassky E, Worm M, Lynde C, Lacour JP, *et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2).* Br J Dermatol. 2021;184(3): 437-49.

3. Hendricks AJ, Yosipovitch G, Shi VY. *Dupilumab use in dermatologic conditions beyond atopic dermatitis - a systematic review.* J Dermatolog Treat. 2021;32(1):19-28.

4. Harb H, Chatila TA. *Mechanisms of Dupilumab. Clin Exp Allergy.* 2020;50(1):5-14.

5. Gandhi NA, Pirozzi G, Graham NMH. *Commonality of the IL-4/IL-13 pathway in atopic diseases.* Expert Review of Clinical Immunology. 2017;13(5):425-37.

6. Eichenfield LF, Flohr C, Sidbury R, Siegfried E, Szalai Z, Galus R, *et al. Efficacy and Safety of Abrocitinib in Combination With Topical Therapy in Adolescents With Moderate-to-Severe Atopic Dermatitis: The JADE TEEN Randomized Clinical Trial.* JAMA Dermatol. 2021;157(10):1165-73.

7. Paller AS, Siegfried EC, Thaçi D, Wollenberg A, Cork MJ, Arkwright PD, *et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial.* J Am Acad Dermatol. 2020;83(5):1282-93.

8. Simpson EL, Paller AS, Siegfried EC, Boguniewicz M, Sher L, Gooderham MJ, *et al. Efficacy and Safety of Dupilumab in Adolescents With Uncontrolled Moderate to Severe Atopic Dermatitis: A Phase 3 Randomized Clinical Trial.* JAMA Dermatol. 2020;156(1):44-56.

9. Fachler T, Shreberk-Hassidim R, Molho-Pessach V. *Dupilumab-induced ocular surface disease: A systematic review.* J Am Acad Dermatol. 2022;86(2):486-7.

10. Neagu N, Dianzani C, Avallone G, Dell'Aquila C, Morariu SH, Zalaudek I, *et al. Dupilumab ocular side effects in patients with atopic dermatitis: a systematic review.* J Eur Acad Dermatol Venereol. 2022.

11. Xiao X, Lin L, Zhu C, Yang X, Ni Y, Zhipeng L, *et al. Efficacy and Safety of Nemolizumab for Treatment of Adult Atopic Dermatitis: A Meta-analysis of Randomized Clinical Trials.* J Investig Allergol Clin Immunol. 2021;31(2):190-2.

12. Tsakok T, Woolf R, Smith CH, Weidinger S, Flohr C. *Atopic dermatitis: the skin barrier and beyond. Br J Dermatol.* 2019;180(3): 464-74.

13. Fadlalmola HA, Albadrani MS, Elhusein AM, Mohamedsalih WE, Swamy VDS, Mamanao DM. *Effectiveness and Safety of Abrocitinib in Patients with Moderate-to-Severe Atopic Dermatitis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials.* Dermatol Res Pract. 2021;2021:8382761.

14. Le M, Berman-Rosa M, Ghazawi FM, Bourcier M, Fiorillo L, Gooderham M, *et al. Systematic Review on the Efficacy and Safety of Oral Janus Kinase Inhibitors for the Treatment of Atopic Dermatitis.* Front Med (Lausanne). 2021;8:682547.

15. Olivera PA, Lasa JS, Bonovas S, Danese S, Peyrin-Biroul *et al. Safety of Janus Kinase Inhibitors in Patients With Inflammatory Bowel Diseases or Other Immune-mediated Diseases: A Systematic Review and Meta-Analysis. Gastroenterology.* 2020;158(6):1554-73.e12.

16. Ytterberg SR, Bhatt DL, Mikuls TR, Koch GG, Fleischmann R, Rivas JL, *et al. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis.* N Engl J Med. 2022;386(4):316-26.

17. Jacquet L, Gaunt DM, Garfield K, Ridd MJ. *Diagnosis, assessment, and treatment of childhood eczema in primary care: cross-sectional study.* BJGP Open. 2017;1(2):bjgpopen 17X1000821.

18. 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(6):850-78.

19. Berth-Jones J, Finlay AY, Zaki I, Tan B, Goodyear H, Lewis-Jones S, *et al. Cyclosporine in severe childhood atopic dermatitis: a multicenter study.* J Am Acad Dermatol. 1996;34(6): 1016-21.

20. Dadlani C, Orlow SJ. *Treatment of children and adolescents with methotrexate, cyclosporine, and etanercept: review of the dermatologic and rheumatologic literature.* J Am Acad Dermatol. 2005;52(2):316-40.

21. Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. Br J Dermatol. 2007;157(1):127-32.

22. Harper JI, Ahmed I, Barclay G, Lacour M, Hoeger P, Cork MJ, *et al. Cyclosporin for severe childhood atopic dermatitis: short course versus continuous therapy.* Br J Dermatol. 2000;142(1): 52-8.

23. Jee SJ, Kim JH, Baek HS, Lee HB, Oh JW. *Long-term Efficacy of Intravenous Immunoglobulin Therapy for Moderate to Severe Childhood Atopic Dermatitis.* Allergy Asthma Immunol Res. 2011;3(2):89-95.

24. LaRosa CL, Quach KA, Koons K, Kunselman AR, Zhu J, Thiboutot DM, *et al. Consumption of dairy in teenagers with and without acne.* J Am Acad Dermatol. 2016;75(2):318-22.

25. Pei AY, Chan HH, Leung TF. *Montelukast in the treatment of children with moderate-to-severe atopic dermatitis: a pilot study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology.* 2001;12(3):154-8.

26. Murphy LA, Atherton D. *A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression.* Br J Dermatol. 2002;147(2): 308-15.

27. 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(3):351-6.

28. Flohr C, Irvine AD. *Systemic therapies for severe atopic dermatitis in children and adults.* The Journal of allergy and clinical immunology. 2013;132(3):774-.e6.

29. Alqarni AM, Zeidler MP. *How does methotrexate work?* Biochem Soc Trans. 2020 ;48(2):559-67.

30. Wang W, Zhou H, Liu L. *Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review.* Eur J Med Chem. 2018; 158:502-16.

31. Becker-Haimes EM, Diaz KI, Haimes BA, Ehrenreich-May J. *Anxiety and Atopic Disease: Comorbidity in a Youth Mental Health Setting.* Child Psychiatry Hum Dev. 2017;48(4):528-36.

32. Davidson WF, Leung DYM, Beck LA, Berin CM, Boguniewicz M, Busse WW, *et al. Report from the National Institute of Allergy and Infectious Diseases workshop on "Atopic dermatitis and the atopic march: Mechanisms and interventions".* The Journal of allergy and clinical immunology. 2019;143(3):894-913.

33. Silverberg JI, Thyssen JP, Fahrbach K, Mickle K, Cappelleri JC, Romero W, *et al. Comparative efficacy and safety of systemic therapies used in moderate-to-severe atopic dermatitis: a systematic literature review and network meta-analysis.* J Eur Acad Dermatol Venereol. 2021;35(9):1797-810.

34. Siegels D, Heratizadeh A, Abraham S, Binnmyr J, Brockow K, Irvine AD, *et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis.* Allergy. 2021;76(4):1053-76.

35. Drucker AM, Ellis AG, Bohdanowicz M, Mashayekhi S, Yiu ZZN, Rochwerg B, *et al. Systemic Immunomodulatory Treatments for Patients With Atopic Dermatitis: A Systematic Review and Network Meta-analysis.* JAMA Dermatol. 2020;156(6):659-67.

ATOPIC DERMATITIS: BEHIND THE ITCH

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Atopic dermatitis (AD), a chronic relapsing inflammatory skin condition, has a wide-ranging impact on patient quality of life. AD is caused by a complex interaction between immune dysregulation, epidermal gene mutations, and environmental factors which disrupt the epidermis, causing intensely pruritic skin lesions. Chronic pruritus (itch) constitutes a heavy burden, with almost a third of the patients in one European study reporting the itch as awful, and half of them as refractory.[1]

Itch, the main symptom in AD, is a challenging issue. Skin lesion distribution is heterogeneous, with on- and outside-lesions.[2] It has a substantial impact on sleep, cognition, appearance (scratching movements and lesions), psychological well-being, quality of life, sexual life, etc. Until now, its mechanism of action has been poorly understood, and the effects of treatment have been disappointing. Itching can be exacerbated by various factors including skin dryness, heat, sweat, contagious itch, anxiety, depression, and stress. In addition, woolen clothes, scratching (itch-scratch cycle), irregular habits, insomnia, nocturnal behaviour, and inflammation can also exacerbate itching.[3]

Itch is caused by a complex interface between skin, keratinocytes, cutaneous nerve fibers, pruritogenic molecules, and the peripheral and central nervous systems. The itch sensation emanates from the activation of nerve endings around the dermo-epidermal junction.[4] These nerve fibers belong to a specialized class of itch-provoking neurons ("pruriceptors") and are characterized by a highly focal spatial activation pattern.[5] Identification of the specific or selective itch receptors in the skin was a major discovery.[6] Itch-mediating primary sensory neurons are equipped with distinct receptors and ion channels for itch transduction, including Mas-related G protein-coupled receptors (Mrgprs), protease-activated receptors, histamine receptors, bile acid receptor, toll-like receptors, and transient receptor potential subfamily V1/A1 (TRPV1/A1).[7, 8]

AD pathogenesis encompasses various immune pathways, and many pruritogenic mediators are at play.[3, 8, 9] The pruritogenic mediators consist of proteases, lipid mediators, neuropeptides, opioids, and various cytokines. Various receptors [transient receptor potential ankyrin 1 (TRPA1), TRPV1, protease-activated receptor-2 (PAR2), gastrin-releasing peptide receptor (GRPR), and Mas-related G proteins], secreted molecules (histamine, nerve growth factor (NGF), substance P (SP), and proteases), and cytokines/chemokines (thymic stromal lymphopoietin (TSLP), interleukin (IL)-2, IL-4, IL-13, and IL-31) are implicated as mediators of chronic pruritus.[9] The role of histamine as a pruritogen is highly debated, and histamine effects may be restricted to acute itch.[10] These chemical mediators originate from complex interactions between keratinocytes, inflammatory cells and nerve endings, coupled with upregulated immune cascades, epidermal barrier function, and potential penetration of Type I allergens into the skin.[11] Several factors, including pH gradient, skin barrier integrity, irritant exposure and the microbiome, modulate the impact of these interactions on neurons.[12] Skin damage from dry skin, genetic lesions, or chronic scratching causes the release of epithelial cell-derived cytokines, such as thymic stromal lymphopoietin (TSLP) and IL-33, which can directly activate the pruriceptors.[13] Keratinocyte-derived proteases, such as kallikreins (KLK)s and cathepsin S, can also trigger itching through cleavage-based activation of the PAR2 and MrgprC11. However, whether KLKs activate neuronal PAR2 directly is not yet clear.[13] Immune cells may modulate itch-sensory neurons through the expression of certain cytokines, such as IL-4 from T helper 2 (Th2) cells, mast cells, and basophils, which can exacerbate the itch sensation in atopic dermatitis. Histamine and tryptase from mast cells and basophils can activate G-protein-coupled receptors such as H1/4R, as well as PAR2. While these receptor–ligand interactions have been linked to itching, and immune cells are known to produce these ligand mediators, the precise cellular sources in the context of specific itch disorders is still under investigation.[13]

TSLP is an IL-7 cytokine produced by keratinocytes and mastocytes. It plays a key role in itching through its specific receptor present on neurons, without lymphocyte intervention.[14] Its production is highly increased in AD and initiates an activated T helper 2 (Th2)-type inflammatory response by dendritic cells.[15] The Orai1/nuclear factor of activated T-cells (NFAT) calcium signaling pathway is an essential regulator of TSLP release from keratinocytes, the primary epithelial cells of the skin. TSLP then acts directly on a subset of TRPA1-positive sensory neurons in order to trigger robust itch behaviors.[15]

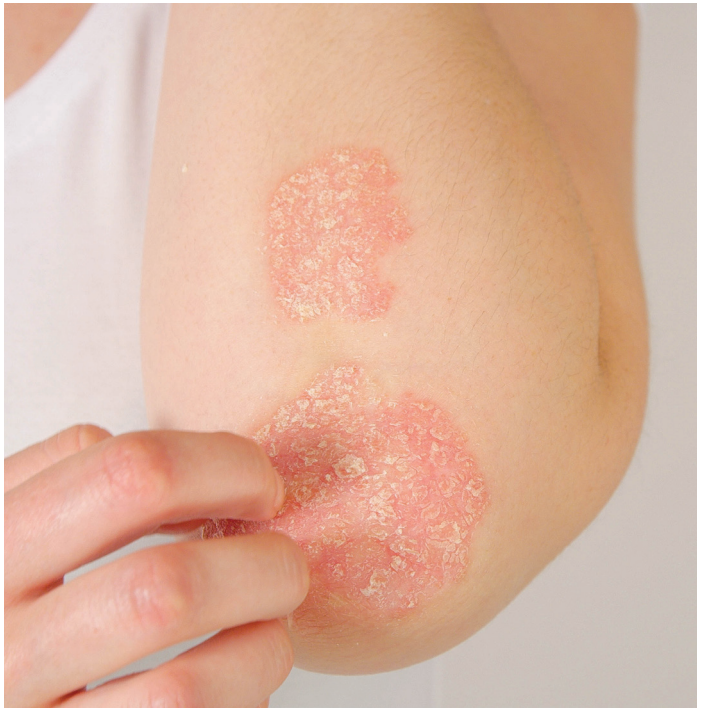
IL-31 is another cytokine that is primarily secreted by activated Th2 cells.[16] IL-31 induces a distinct transcriptional program in sensory neurons and the outgrowth of sensory neurons in a STAT3-dependent manner.[17] The IL-31 translational effect (nerve elongation) may be involved in skin hypersensitivity to pruritogenic trigger factors, especially in patients with AD.[17] **Prolonged itch may be initiated by the overexpression of IL-31 and the promotion of sensory neuronal outgrowth and stimulation.[18]**

Type 2 immune inflammation, the dominant pathway involved in itching, is driven by innate type 2 ILC and Th2 cells as well as their cytokines, such as IL-4 and IL-13.[19] Il-4 and IL-3 directly activate sensory neurons in both mice and humans.[10] Chronic itch is dependent on neuronal IL-4Rα and Janus kinase 1 (JAK1) signaling.[10] Patients with recalcitrant chronic itch that failed other immunosuppressive therapies markedly improved when treated with JAK inhibitors.[10]

Histological investigations have shown that the density of epidermal nerve fibers is higher in the skin of patients with AD.[20, 21] Epidermal hyperinnervation is probably caused by an imbalance between nerve elongation factors, such as nerve growth factor (NGF), and nerve repulsion factors, such as semaphorin 3A (Sema3A), produced by keratinocytes.[22]

Chronic itch has parallels with chronic pain.[23] Chronic itch can be associated with spontaneous itching, hyperknesis (enhanced itch to a normally itchy stimulus), and alloknesis (itch elicited by an innocuous touch stimulus).

Three general mechanisms may contribute to chronic itch: peripheral sensitization which may occur through PAR-2, central sensitization which may occur through TLR3, and dysfunction of inhibitory interneurons.[24]



Barrier function has long been known to be reduced in the skin of patients with AD. **Filaggrin (FLG) has a key structural and functional role in the epidermis and is important for the formation of the corneocyte, as well as the generation of its intracellular metabolites, which contribute to stratum corneum hydration and pH.** A well-functioning epidermis protects humans from exogenous stressors and helps maintain internal fluid and electrolyte homeostasis. Loss-of-function mutations in the FLG gene result in either a reduction (heterozygous) or complete absence (homozygous) of epidermal FLG and its degradation products, which lead to dysfunction of the epidermis and reduced barrier function.[12, 25]

Itch triggers a need to scratch. Scratching temporarily relieves itch sensations through the activation of pain-sensory fibers, which can inhibit itch sensations at the level of the spinal cord.[26] However, chronic itch sensations can drive persistent scratching responses that, in turn, cause mechanical disruption of the skin. Chronic itch sensations and associated scratching behaviors are components of a dynamic pathological process known as the itch–scratch cycle.[13]

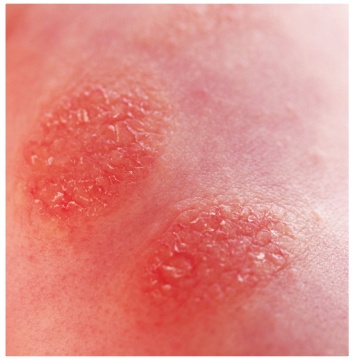
Scratching behaviors exacerbate itch sensation through damage to skin epithelial cells. The epithelial stress response releases cytokines, proteases, and antimicrobial peptides (AMP)s that can activate immune cells to promote inflammation. Keratinocytes may also activate itch-sensory neurons directly through soluble mediators such as cytokines and proteases. Release of neuropeptides from neurons can also cause neurogenic inflammation. In contrast, cytokines and proteases produced by immune cells interface with the sensory nervous system in order to mediate itch.[13]

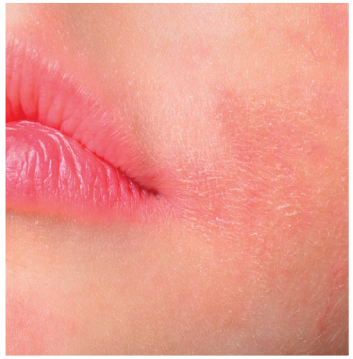
Management of itching and pain in AD is mostly based on topical therapy, although other therapeutic options such as systemic drugs, phototherapy, balneotherapy, and control of environmental triggers are available.[27] Current progress in the knowledge of the itch process, as well as of the numerous mediators and receptors involved, has led to a large variety of possible therapeutic pathways. Currently, inhibitors of IL-31, IL-4/13, neurokinin-1 (NK1) receptors, opioids and cannabinoids, JAK, phosphodiesterase-4-inhibitor (PDE4) or TRP are the main compounds involved in clinical trials. However, many new targets, such as Mas-related G protein-coupled receptors (GPCR)s and unexpected new pathways must also be explored.[27]

Treating chronic pruritus needs to be targeted, multimodal, and performed in a step-wise procedure, requiring an interdisciplinary approach. The updated and consensus-based (S2k) European guideline on chronic pruritus, which provides AD-specific guidelines, was published in 2019.[28]

A position paper on itch and pain management in AD was co-authored by eleven members of the International Society of Atopic Dermatitis (ISAD/Oriented Patient-Education Network in Dermatology (OPENED) task force and published in 2021.[29]

In conclusion, the understanding of the itch process is constantly expanding. A holistic approach to treating AD patients is essential. In any case, it is beneficial to break the itch/scratching cycle.[3, 29]





KEY MESSAGES

- Itch is the main concern for patients with atopic dermatitis (and their relatives/friends)
- Research on itching (especially in atopic dermatitis) provides numerous targets for the alleviation of itch
- Emollients are useful for both skin dryness and itch alleviation

REFERENCES

1. Steinke S, Zeidler C, Riepe C, Bruland P, Soto-Rey I, Storck M, *et al. Humanistic burden of chronic pruritus in patients with inflammatory dermatoses: Results of the European Academy of Dermatology and Venereology Network on Assessment of Severity and Burden of Pruritus (PruNet) cross-sectional trial.* J Am Acad Dermatol. 2018;79(3):457-63 e5.

2. Silverberg JI, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, *et al. Distribution of atopic dermatitis lesions in United States adults.* J Eur Acad Dermatol Venereol. 2019;33(7):1341-8.

3. Murota H, Katayama I. *Exacerbating factors of itch in atopic dermatitis.* Allergol Int. 2017;66(1):8-13.

4. Misery L, Brenaut E, Le Garrec R, Abasq C, Genestet S, Marcorelles P, *et al. Neuropathic pruritus.* Nat Rev Neurol. 2014;10(7):408-16.

5. Lin SH, Steinhoff M, Ikoma A, Chang YC, Cheng YR, Chandra Kopparaju R, *et al. Involvement of TRPV1 and TDAG8 in Pruriception Associated with Noxious Acidosis.* J Invest Dermatol. 2017;137(1):170-8.

6. Steinhoff M, Neisius U, Ikoma A, Fartasch M, Heyer G, Skov PS, *et al. Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin.* J Neurosci. 2003;23(15):6176-80.

7. Liu T, Ji RR. *New insights into the mechanisms of itch: are pain and itch controlled by distinct mechanisms?* Pflugers Arch. 2013;465(12):1671-85.

8. Ji RR. *Neuroimmune interactions in itch: Do chronic itch, chronic pain, and chronic cough share similar mechanisms?* Pulm Pharmacol Ther. 2015;35:81-6.

9. Mollanazar NK, Smith PK, Yosipovitch G. *Mediators of Chronic Pruritus in Atopic Dermatitis: Getting the Itch Out?* Clin Rev Allergy Immunol. 2016;51(3):263-92.

10. Oetjen LK, Mack MR, Feng J, Whelan TM, Niu H, Guo CJ, *et al. Sensory Neurons Co-opt Classical Immune Signaling Pathways to Mediate Chronic Itch.* Cell. 2017;171(1):217-28 e13.

11. Pinho-Ribeiro FA, Verri WA, Jr., Chiu IM. *Nociceptor Sensory Neuron-Immune Interactions in Pain and Inflammation.* Trends Immunol. 2017;38(1):5-19.

12. Yosipovitch G, Misery L, Proksch E, Metz M, Stander S, Schmelz M. *Skin Barrier Damage and Itch: Review of Mechanisms, Topical Management and Future Directions.* Acta Derm Venereol. 2019;99(13):1201-9.

13. Mack MR, Kim BS. *The Itch-Scratch Cycle: A Neuroimmune Perspective.* Trends Immunol. 2018;39(12):980-91.

14. Misery L. *[TSLP, the key of pruritus in atopic dermatitis].* Med Sci (Paris). 2014;30(2):142-4.

15. Wilson SR, The L, Batia LM, Beattie K, Katibah GE, McClain SP, *et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch.* Cell. 2013;155(2):285-95.

16. Dillon SR, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, *et al. Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice.* Nat Immunol. 2004;5(7):752-60.

17. Feld M, Garcia R, Buddenkotte J, Katayama S, Lewis K, Muirhead G, *et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves.* J Allergy Clin Immunol. 2016;138(2):500-8 e24.

18. Nakashima C, Otsuka A, Kabashima K. *Interleukin-31 and interleukin-31 receptor: New therapeutic targets for atopic dermatitis.* Exp Dermatol. 2018;27(4):327-31.

19. Moniaga CS, Tominaga M, Takamori K. *The Pathology of Type 2 Inflammation-Associated Itch in Atopic Dermatitis.* Diagnostics (Basel). 2021;11(11):2090.

20. Ikoma A, Steinhoff M, Ständer S, Yosipovitch G, Schmelz M. *The neurobiology of itch.* Nat Rev Neurosci. 2006;7(7):535-47.

21. Tominaga M, Takamori K. *Recent advances in pathophysiological mechanisms of itch.* Expert Rev Dermatol. 2010;5:197-212.

22. Tominaga M, Takamori K. *An update on peripheral mechanisms and treatments of itch.* Biol Pharm Bull. 2013;36(8):1241-7.

23. Yosipovitch G, Carstens E, McGlone F. *Chronic itch and chronic pain: Analogous mechanisms.* Pain. 2007;131(1-2):4-7.

24. Akiyama T, Carstens E. *Neural processing of itch.* Neuroscience. 2013;250:697-714.

25. McPherson T. *Current Understanding in Pathogenesis of Atopic Dermatitis.* Indian J Dermatol. 2016;61(6):649-55.

26. Ross SE. *Pain and itch: insights into the neural circuits of aversive somatosensation in health and disease.* Curr Opin Neurobiol. 2011;21(6):880-7.

27. Misery L, Brenaut E, Pierre O, Le Garrec R, Gouin O, Lebonvallet N, *et al. Chronic itch: emerging treatments following new research concepts.* Br J Pharmacol. 2021;178(24):4775-91.

28. Weisshaar E, Szepietowski JC, Dalgard FJ, Garcovich S, Gieler U, Gimenez-Arnau AM, *et al. European S2k Guideline on Chronic Pruritus.* Acta Derm Venereol. 2019;99(5):469-506.

29. Misery L, Belloni Fortina A, El Hachem M, Chernyshov P, von Kobyletzki L, Heratizadeh A, *et al. A position paper on the management of itch and pain in atopic dermatitis from the International Society of Atopic Dermatitis (ISAD)/Oriented Patient-Education Network in Dermatology (OPENED) task force.* J Eur Acad Dermatol Venereol. 2021;35(4):787-96.

THE ROLE OF SKIN CARE IN THE MANAGEMENT OF ATOPIC DERMATITIS: IMPACT ON THE SKIN BARRIER

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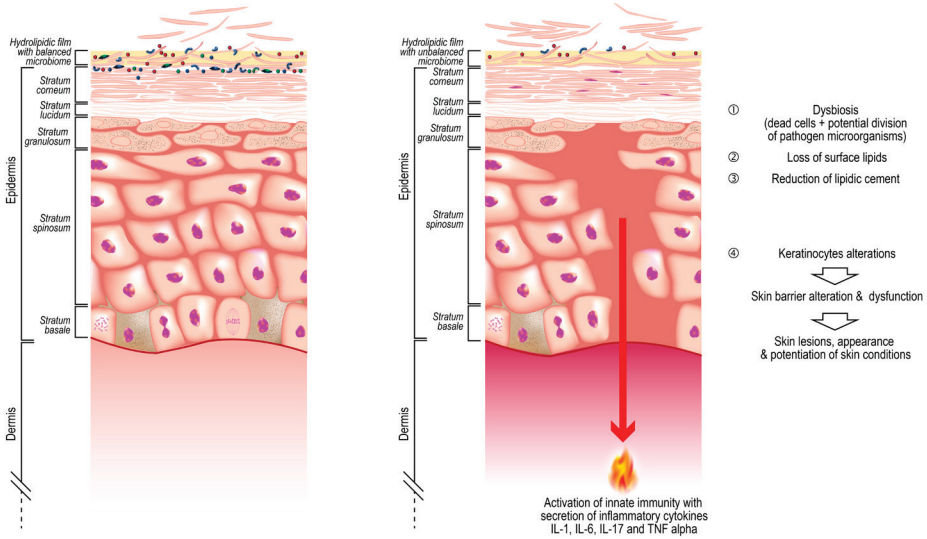
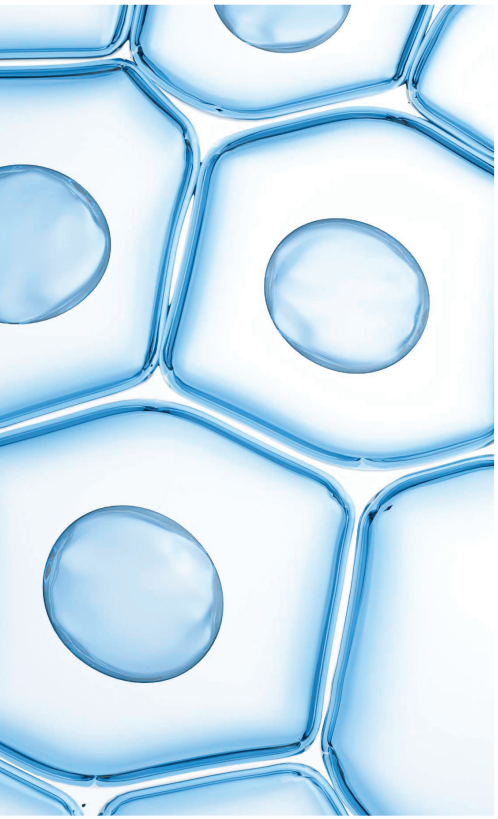
The primary role of the skin is to serve as a barrier, protecting the body from a potential assault from microorganisms, toxic substances and other external physical, chemical or organic factors and to limit transepidermal water loss (TEWL).[1, 2]

In healthy skin, the predominance of hydrophobic substances (lipidic cement) in the intercellular constituents is a significant factor regulating the enzymatic activity and dehydration of the skin. Together with the intracellular constituents, the hydrophilic film is present on the skin as an emulsion and formed from sweat and sebum excretion. It covers the epidermis, thus strengthening the cutaneous barrier and helping the skin to defend the body against TEWL or hyperhydration, particularly during climatic changes.[3] Ceramides are bound to cornified envelope proteins and form the backbone for the subsequent addition of free ceramides, free fatty acids and cholesterol in the Stratum Corneum, while filaggrin is cross-linked to the cornified envelope and aggregates keratin filaments into macrofibrils.[4, 5]





Atopic dermatitis (AD) is the most common chronic inflammatory skin disease.[6] Genetic predisposition, epidermal barrier disruption, and dysregulation of the immune system are some of the critical components of AD. Changes in epidermal differentiation and lipid composition lead to a disrupted skin barrier, through a deficiency of barrier proteins, including involucre and tight junction proteins, a modified pH and dysbiosis, a change in the diversity of the skin microbiota with an increase of *Staphylococcus aureus* during flares and an alteration of the immune response leading to the onset or worsening of AD (*Figure 1*).[7]

A such impaired skin barrier enhances allergen penetration into the skin, reduces the natural moisturizing factor (NMF) linked to the filaggrin deficiency, leads to skin inflammation and clinical signs of AD and increases TEWL, related to the deficiency of the hydrolipidic film and inadequate ceramides/cholesterol ratio.[8]

Frequent application of appropriate moisturizers and emollients, such as physiologic lipid mixtures and ceramide-dominant lipid, helps to reduce TEWL, enhances skin hydration, decreases bacterial colonization, and improves skin barrier function, resulting in a decreased need for topical corticosteroid therapy.[8, 9]

International guidelines for the treatment of AD recommend the regular use of moisturizers.[8, 10] Globally, moisturizers include emollients, humectants, and occlusive agents. European guidelines recommend the prescription of moisturizers in adequate amounts, and with a liberal and frequent use in both children and adults.[8] Products with a higher lipid content should always be preferred during winter. In mild-to-moderate AD, a regular use of emollient has been shown to be beneficial as a short- and long-term steroid sparing effect. However, an induction of remission with topical corticosteroids or topical calcineurin inhibitors is required first. US guidelines recommend the application of moisturizers as being an integral part of the treatment of patients with AD, with strong evidence that their use reduces disease severity and the need for pharmacologic intervention.[10]

According to these and other guidelines, moisturizers should be applied daily.[8, 10-13] Moreover, an optimal quantity is recommended to improve the course of AD.[14] Fleischer et al. suggests that in children 150 to 200 g/week and in adults 500 g/week of a moisturizer, 125 to 250 g of an ointment in children and 260 to 330 g in adults and 140 to 275 g of a cream in children and 290 to 330 g in adults are optimal quantities to be applied per week. **Despite these clear indications of guidelines and publications, different studies have shown that only one out of three AD patients is compliant with the topical treatment prescribed and one out of two uses less quantity of emollients than actually recommended.[15, 16]**

To date, different types of emollients exist, that contain, among other components, ceramides and cholesterol to restore an effective skin barrier, phytosphingosine which is a natural constituent of ceramides and which stimulates the production of new lipids, as well as essential fatty acids and colloidal oatmeal which has anti-pruritic, anti-inflammatory and antioxidant properties.[17-19]

Particularly in AD, moisturizers require a strong necessity for efficacy, extreme tolerance, the absence of side effects such as burning or tickling sensations, and an excellent sensoriality in order to encourage compliance and thus to be able to provide long-lasting benefit.

As an example, a specific moisturizer (Atoderm® Intensive baume) has been developed by Laboratoires NAOS. This moisturizer contains the Lipigenium™ complex made of phytosphingosine which helps the skin to rebuild its barrier by activating the ceramid neosynthesis and which has been shown to restore the filaggrin expression 37-times over after seven days.[20, 21] Moreover, it contains biomimetic lipids (ceramides 1, 3 & 6, cholesterol, essential fatty acids) that replenish the lipid barrier, enoxolone, which has anti-inflammatory and anti-itching properties through a reduction of the TSLP expression by epidermal cells in atopic environment and palmitoylethanolamide which is anti-itching and improves the skin comfort and quality of life of patients.[22-24] A yet unpublished 6-month study in 130 patients with moderate AD and aged between 6 months and 15 years confirmed that the physician and patient/caregiver SCORAD score had significantly ($p<0.05$) decreased after 6 months, with the patient SCORAD score having significantly changed already after 4 months ($p=0.0086$). Moreover, the patients' quality of life using the IDQoL score had significantly ($p=0.0337$) improved by 89% from baseline at the end

of the study; 76% of the subjects reported no relapse of their AD after 6 months and time to relapse was delayed by more than 20 days in those patients who did relapse.

Another unpublished clinical study testing the anti-itching properties of a gel formulation containing the Lipigenium™ complex showed that the average auto-itching score immediately and significantly ($p<0.0001$) decreased by 18% after the first application and continued to decrease after one (-46%) and 21 days (-70%).

In addition to moisturizing the skin, cleansing of the skin using specifically adapted products (neutral to low pH, hypoallergenic, and fragrance free) plays a key role in the general management of AD. The skin must be cleansed thoroughly but gently and carefully, in order to get rid of crusts and mechanically eliminate bacterial contaminants in the case of bacterial super-infection. Bath oils are a valuable addition for skin care, especially in babies and children.[8, 10]

It is important that the skin be dried gently after bathing and that emollients are applied systematically afterwards, to improve the skin barrier function and to moisturize the skin.[25, 26]

KEY MESSAGES

- Skincare products are useful in the protection and the reinforcement of the skin barrier for patients with atopic dermatitis
- Skincare must include both emollients and cleansing/bathing products
- Topical therapy has to be adapted to the specific needs of each single patient
- Emollients and cleansing products need to be well tolerated and pleasant to use, in order to encourage suitable compliance from the patients

REFERENCES

1. Grice EA, Segre JA. *The skin microbiome. Nature reviews Microbiology.* 2011;9(4): 244-53.

2. Grice EA. *The skin microbiome: potential for novel diagnostic and therapeutic approaches to cutaneous disease.* Semin Cutan Med Surg. 2014;33(2):98-103.

3. Pons-Guiraud A. *Dry skin in dermatology: a complex physiopathology.* J Eur Acad Dermatol Venereol. 2007;21 Suppl 2:1-4.

4. Proksch E, Brandner JM, Jensen JM. *The skin: an indispensable barrier.* Exp Dermatol. 2008;17(12):1063-72.

5. Jensen JM, Proksch E. *The skin's barrier.* G Ital Dermatol Venereol. 2009;144(6): 689-700.

6. Ständer S. *Atopic Dermatitis.* N Engl J Med. 2021;384(12):1136-43.

7. Kim J, Kim BE, Leung DYM. *Pathophysiology of atopic dermatitis: Clinical implications.* Allergy Asthma Proc. 2019;40(2):84-92.

8. 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(6): 850-78.

9. Kim BE, Leung DYM. *Significance of Skin Barrier Dysfunction in Atopic Dermatitis.* Allergy Asthma Immunol Res. 2018;10(3): 207-15.

10. Eichenfield LF, Tom WL, Berger TG, Krol A, Paller AS, Schwarzenberger K, *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(1): 116-32.

11. Schneider L, Tilles S, Lio P, Boguniewicz M, Beck L, LeBovidge J, *et al. Atopic dermatitis: a practice parameter update 2012.* J Allergy Clin Immunol. 2013;131(2):295-9.e1-27.

12. Ring J, Alomar A, Bieber T, Deleuran M, Fink-Wagner A, Gelmetti C, *et al. Guidelines for treatment of atopic eczema (atopic dermatitis) Part II.* J Eur Acad Dermatol Venereol. 2012;26(9):1176-93.

13. 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(1):152-69.

14. Fleischer DM, Udkoff J, Borok J, Friedman A, Nicol N, Bienstock J, *et al. Atopic dermatitis: skin care and topical therapies.* Semin Cutan Med Surg. 2017;36(3):104-10.

15. Aubert H, Barbarot S. *[Non adherence and topical steroids].* Ann Dermatol Venereol. 2012;139 Suppl 1:S7-12.

16. Choi JY, Dawe R, Ibbotson S, Fleming C, Doney A, Foerster J. *Quantitative analysis of topical treatments in atopic dermatitis: unexpectedly low use of emollients and strong correlation of topical corticosteroid use both with depression and concurrent asthma.* Br J Dermatol. 2020;182(4):1017-25.

17. Capone K, Kirchner F, Klein SL, Tierney NK. *Effects of Colloidal Oatmeal Topical Atopic Dermatitis Cream on Skin Microbiome and Skin Barrier Properties.* J Drugs Dermatol. 2020;19(5):524-31.

18. Školová B, Kováčik A, Tesař O, Opálka L, Vávrová K. *Phytosphingosine, sphingosine and dihydrosphingosine ceramides in model skin lipid membranes: permeability and biophysics.* Biochim Biophys Acta Biomembr. 2017;1859(5):824-34.

19. Wohlrab J, Gebert A, Neubert RHH. *Lipids in the Skin and pH.* Curr Probl Dermatol. 2018;54:64-70.

20. Choi HK, Cho YH, Lee EO, Kim JW, Park CS. *Phytosphingosine enhances moisture level in human skin barrier through stimulation of the filaggrin biosynthesis and degradation leading to NMF formation.* Arch Dermatol Res. 2017;309(10):795-803.

21. Choi GH, Wahid F, Kim YY. *The effect of a phytosphingosine-like substance isolated from Asterina pectinifera on involucrin expression in mite antigen-stimulated HaCaT cells.* Nat Prod Commun. 2010;5(7):1081-4.

22. Liu YJ. *Thymic stromal lymphopoietin: master switch for allergic inflammation.* J Exp Med. 2006;203(2):269-73.

23. Kowalska A, Kalinowska-Lis U. *18β-Glycyrrhetinic acid: its core biological properties and dermatological applications.* Int J Cosmet Sci. 2019;41(4):325-31.

24. Eberlein B, Eicke C, Reinhardt HW, Ring J. *Adjuvant treatment of atopic eczema: assessment of an emollient containing N-palmitoylethanolamine (ATOPA study).* J Eur Acad Dermatol Venereol. 2008;22(1): 73-82.

25. 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.

26. Berardesca E, Mortillo S, Cameli N, Ardigo M, Mariano M. *Efficacy of a shower cream and a lotion with skin-identical lipids in healthy subjects with atopic dry skin.* J Cosmet Dermatol. 2018;17(3):477-83.

NOTES

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