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Claudia Hülpüsch, Andreas B. Weins, Claudia Traidl-Hoffmann, Matthias Reiger

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REVIEW ARTICLE

A new era of atopic eczema research: Advances and highlights

Claudia Hülpüsch[1,2,3] | Andreas B. Weins[4] | Claudia Traidl-Hoffmann[1,2,3,5] | Matthias Reiger[1,2,3]

[1]Department of Environmental Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany

[2]Institute of Environmental Medicine, Helmholtz Zentrum München, Augsburg, Germany

[3]CK CARE – Christine Kühne Center for Allergy research and Education, Davos, Switzerland

[4]Department of Dermatology, Faculty of Medicine, University of Augsburg, Augsburg, Germany

[5]ZIEL, Technical University of Munich, Freising, Germany

Correspondence
Claudia Traidl-Hoffmann, Department of Environmental Medicine, Faculty of Medicine, University of Augsburg, and Helmholtz Zentrum München, Neusäßer Str. 47, D-86156 Augsburg, Germany.
Email: claudia.traidl-hoffmann@med.uni-augsburg.de

Abstract

Atopic eczema (AE) is an inflammatory skin disease with involvement of genetic, immunological and environmental factors. One hallmark of AE is a skin barrier disruption on multiple, highly interconnected levels: filaggrin mutations, increased skin pH and a microbiome dysbiosis towards *Staphylococcus aureus* overgrowth are observed in addition to an abnormal type 2 immune response. Extrinsic factors seem to play a major role in the development of AE. As AE is a first step in the atopic march, its prevention and appropriate treatment are essential. Although standard therapy remains topical treatment, powerful systemic treatment options emerged in the last years. However, thorough endotyping of the individual patients is still required for ideal precision medicine approaches in future. Therefore, novel microbial and immunological biomarkers were described recently for the prediction of disease development and treatment response. This review summarizes the current state of the art in AE research.

KEYWORDS
atopic dermatitis, biomarkers, personalized medicine, therapy

1 | INTRODUCTION

Atopic eczema (AE) or atopic dermatitis (AD) is an inflammatory skin disease with involvement of genetic, immunological and environmental factors which are highly interconnected.[1,2] The heterogenic disease can be separated into different phenotypes and clinical presentations defined by the ethnicity, disease onset, disease severity, chronic vs acute, intrinsic vs extrinsic (IgE level), paediatric vs adult and inflammatory signature.[3-5] A common feature of all subtypes is a tremendous psychosocial burden for all patients with AE.[6] Prevalence varies by area and is reported to be 15–20% in children in Europe, persisting in up to 5–10% of adults.[7-9] Although severe cases are less abundant than mild or moderate disease pattern, 2% of affected children are severely suffering.[7,9] Therefore, AE remains to be a high and even increasing socio-economic burden in the United States and in Europe,[10,11] whereas slightly decreasing numbers were reported over the last few years in Japan.[12] Children often overcome atopic eczema, but set off on the so-called 'atopic march', that is begin a classic 'allergy career'. Scientifically, AE is a risk factor for the development of allergies. These are primarily type I allergies with clinical features such as hay fever and asthma. Allergies are increasingly becoming a widespread disease. Currently, almost every fourth person in Europe suffers from symptoms such as asthma or hay fever and the associated restrictions in everyday life or at work. For society, the reduced ability to perform at school, university and at work means great socio-economic damage.[13,14]

2 | ATOPIC ECZEMA AS AN ENVIRONMENTAL DISEASE

The picture of the reasons for the rapid increase in allergies and atopic diseases remains incomplete to this day. For sure, it cannot be explained by genetics alone.[15] In fact, AE can potentially be seen as an environmental disease occurring in susceptible individuals.[16-18] A variety of intrinsic and extrinsic risk factors were identified to influence

AE development and exacerbation (Figure 1).[19] Intrinsic risk factors for AE include parental atopic history, filaggrin (FLG) mutations, polysensitization, decreased short-chain fatty acids in the gut of children, and underlying medical conditions as keratoconus.[20-25] However, extrinsic factors as low microbial exposure and diversity, antibiotic exposure, urban environment, tobacco smoke exposure, stress, food and pollutants are as important for AE development.[16] The lower and later exposure to microbes is described by the 'hygiene' or 'old friends' hypothesis and is associated with increased allergy prevalence.[26-28] The relationship between host and microbes is symbiotic and bacteria shape essential biological functions such as the development of a tolerogenic immune response towards commensals.[29] In line, the prevalence of AE was reported to be higher in urban than in rural areas.[30] The hygiene theory could be supported recently in a birth cohort—siblings, infections and pet—especially dog keeping—were protective for AE.[28,31] However, contradicting results exist on the influence of dog and cat ownership on disease development.[32,33] Also, caesarean section birth with lower microbial exposure could recently not be confirmed to have a higher risk for AE than vaginal delivery,[34] whereas very preterm birth even seems to be associated with decreased risk for AE development.[20,21] A deeper understanding of the complex interplay between microbes and host is still needed.[35] Another environmental factor is the surrounding climate in a given location, a combination of temperature, and precipitation and therefore UV exposure and humidity.[16] Although contradicting reports exist on the influence of the single factors on AE development and exacerbation, they seem to be worth further investigation, especially in times of climate change.[16,36] These factors also influence sweat production, which promotes itch in AE.[37] Also, water hardness and detergent usage impact AE.[9,38] The patient's residence also determines the exposure to airborne trigger factors as aeroallergens and air pollutants which are associated with AE development and exacerbation. Especially, aeroallergens from house dust mite, pollen and pet dander caused positive patch tests and delayed cutaneous response in AE patients to a higher extent than in healthy controls.[39] One major component of environmental air pollutants is Diesel exhaust particles, which triggers an itch-scratch response by binding to the aryl hydrocarbon receptor (AhR).[40-42] Children seem to be more vulnerable than adults to pollution as an AE exacerbation trigger.[43] The stress level coming from the psychosocial environment is another extrinsic factor, which is correlated with disease symptom severity and exacerbation,[6] leading to a vicious circle as AE is a strong psychological burden for patients.[44,45] In line, psychological interventions had a positive effect on AE severity in a meta-analysis and were also associated with other allergic diseases.[46,47]

Milestones

- Environmental risk factors are important in AE development
- Recognition of the complex interplay between environment and host-microbe
- Discovery of biomarkers as TARC and the microbiome for AE progression
- Biologics strongly improve symptom severity
- Recognition of the disease diversity is reflected in the variety of novel therapy targets

Outlook

- Targeting *S. aureus* or its communication system as leverage point for local AE treatment
- *S. aureus* vaccines could improve the patient situation
- Efficacy of AE prevention, for example with emollients and pre- and probiotics is still controversial but could be an essential tool to stop the atopic march
- Investigation of active modulation of the skin barrier (eg pH) and the immune system (eg Vitamin D3, sport, food) should be in focus
- Time frame and trigger factors for AE development must be further investigated

3 | ATOPIC MARCH AND DISEASE PERSISTENCE

Not in all cases of childhood AE, the disease persists to adulthood. Risk factors for persistence are predicted by disease severity and vascular endothelial growth factor (VEGF) serum levels at three years[4] as well as by early-onset and high IL-13 levels.[48,49] Furthermore, the risk to develop allergic rhinitis—especially in untreated AE[49]— or adult-onset asthma is significantly higher in patients with allergic diseases and AE.[50] Therefore, AE is claimed to be the first step of the so-called atopic march.[51] Underlying skin barrier defects in AE facilitate the penetration of allergens and irritants and can thereby lead to food allergy, allergic rhinitis, and/or allergic asthma.[13] A signature of eight genes (CLC, EMR4P, IL5RA, FRRS1, HRH4, SLC29A1, SIGLEC8 and IL1RL1) identifies multimorbidity for asthma, rhinitis and AE, suggesting that multimorbidity is mechanistically different to single allergic diseases.[52] The fact that AE itself is a risk factor for the development of allergies also means that the treatment of this chronic inflammatory skin disease can be a prevention of other atopic diseases.

4 | BASIC MECHANISMS AND POTENTIAL TARGETS

4.1 | Disturbed skin barrier (FLG, pH, microbiome)

The skin barrier in AE is disturbed on multiple levels, including physical, chemical, immunological, neurologic and microbial components.[1]

Martin et al. recently summarized genetic risk factors for AE, many of them belonging to extracellular matrix components and its modulators (eg FLG, COL5A3, COL6A6 and MMP9, TMEM79).[53,54] A variety of AE mice models are used to investigate skin barrier defects, among them FLG flaky tail (ft)/ft mice,[55] Hrnr−/− mice[56] and

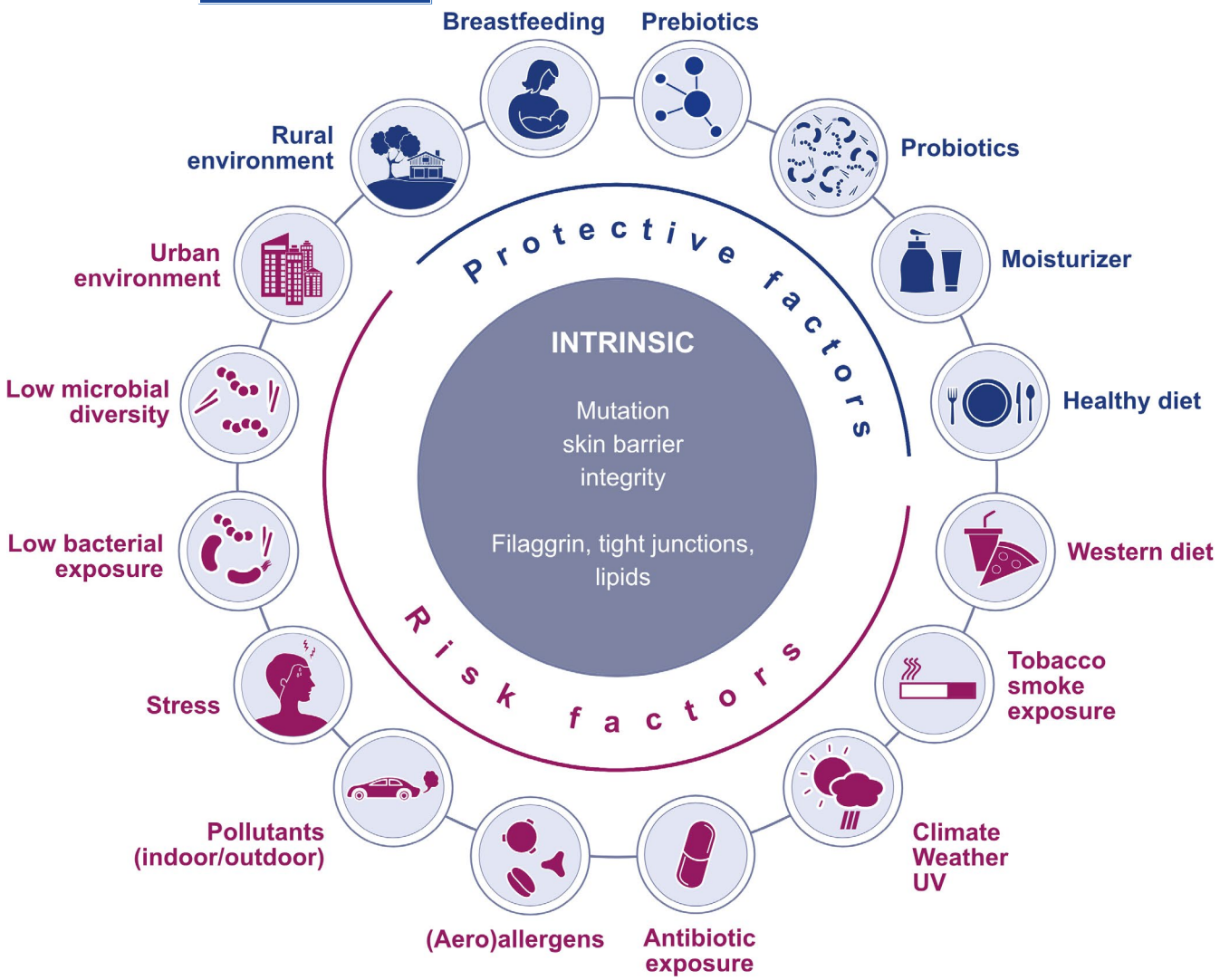

FIGURE 1 Risk and protective factor for atopic dermatitis. Known extrinsic risk factors (red) and protective factors (blue) for atopic dermatitis are summarized in this figure

TMEM79−/− mice.[54] One major genetic predisposition for the development of AE are loss-of-function mutations in the skin barrier gene filaggrin.[57] Degradation products of histidine-rich filaggrin support the healthy skin barrier as natural moisturizing factors (NMF) and simultaneously maintain an acidic skin pH.[58] The skin pH in AE and especially AE lesions was reported to be increased.[59] In line, an acidic skin pH is associated with low scaling and high hydration, whereas alkaline skin pH is associated with skin barrier dysfunction and decreased stratum corneum integrity.[60,61] Alkalization of the skin pH directly modulates the activity of the stratum corneum located serine protease kallikrein 5 (KLK5) which has the ability to degrade cell junction proteins, leading to barrier dysfunction and itch.[62] Recently, exogenic mutations in the KLK5 inhibitor Lympho-epithelial Kazal-type-related inhibitor (LEKTI) were associated with AE, supporting the importance of protease activity in the disease.[63] Furthermore, the lipid composition of the skin is abnormal in AE. Changes in ceramides and free fatty acids were reported, the latter correlating with the skin microbiome composition.[64,65]

A skin microbiome dysbiosis towards *Staphylococcus aureus* and decreased microbial diversity is another hallmark of AE.[66] The intrinsic and extrinsic factors shaping the skin microbiome are complex and yet poorly understood.[35] However, several factors relevant in AE are known to influence the microbiome. The acidic skin pH of healthy skin for example limits the growth of harmful skin bacteria as *S. aureus* and enhances the growth of the commensal *S. epidermidis*.[67,68] Genetics also shape the skin microbiome as recently shown in a mouse model: wild-type and Flg ft/ft mice significantly differed in the skin microbiome composition, revealing less diversity with an increased staphylococci colonization.[55] In this study, AE did not develop under germ-free conditions but was dependent on microbial colonization and subsequent IL-1beta induction.[55] Both alpha-diversity and *S. aureus* abundance correlate with disease severity. However, this association seems to depend on the skin site and could be shown for the thigh but not the back of AE patients in a recent study.[69] Not only the presence of *S. aureus* but also capability of *S. aureus* strains to produce biofilm and toxins is associated

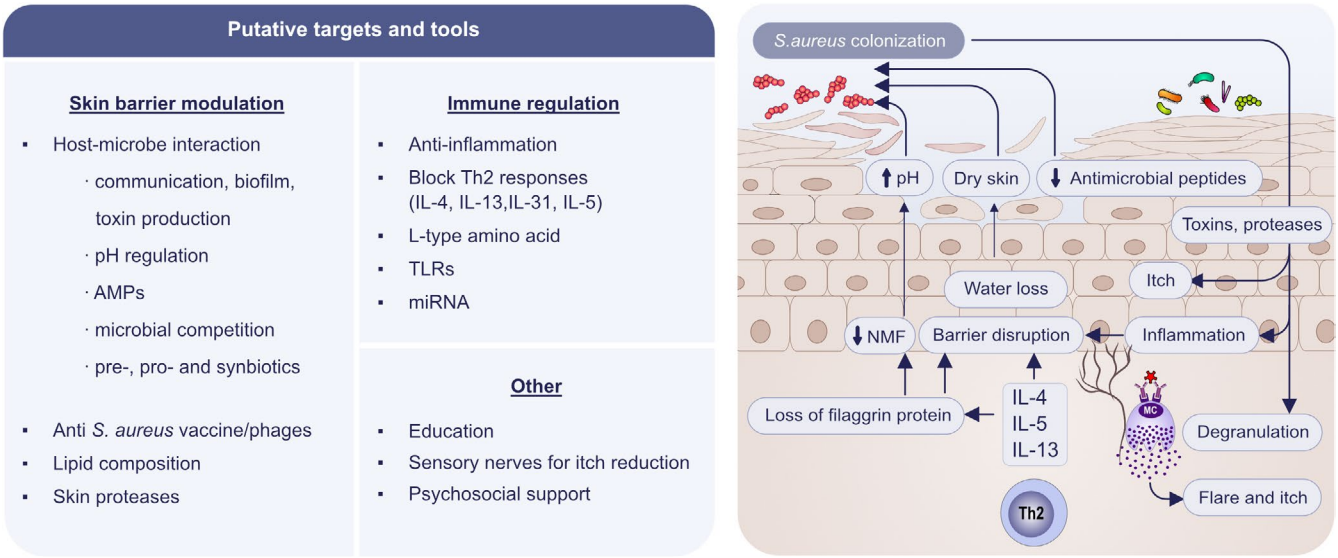

FIGURE 2 Leverage points for (future) atopic dermatitis therapies. In atopic dermatitis, the skin barrier is disturbed on multiple levels and could be used for atopic dermatitis treatments in future. AMP, Antimicrobial peptides; IL, Interleukin; miRNA, micro RNA; NMF, Natural moisturizing Factors; Th2, T-helper 2 TLR, Toll-like receptor

with AE severity.[66,70,71] *S. aureus* activates the immune system in AE among others by the expression of proteases, toxins, superantigens and other virulence factors[66,72] (Figure 2). Interestingly, cigarette smoke redirects *S. aureus* towards virulence factor associated with persisting infection and could therefore explain the avoidable risk factor of tobacco smoke for AE.[25,73] The virulence factors trigger a vicious cycle in AE. The stimulation of the immune system shapes the inflammatory environment, the expression of IL-31 causes itch and the resulting scratching further damages the skin barrier. The complex interaction between *S. aureus* and the innate and adaptive immune system has been nicely summarized by Yoshikawa et al 2019.[66]

In the context of itch and scratch response, sensory neurons are important.[74] However, the nervous system is not only responsible for pruritus, but also modulates the immune response in AE.[75]

4.2 | Immune system

The disturbed skin barrier in AE facilitates the entrance of allergens which are presented by antigen-presenting cells in the lymph nodes to naïve T cells, which in the presence of, for example, thymic stromal lymphopoietin (TSLP) differentiate into allergen-specific T-helper cells. These cells release IL-4, IL-13 and IL-5—a major hallmark in AE—which lead to even stronger epithelial skin barrier disruption by downregulation of filaggrin and claudins and recruitment of eosinophils.[76-79] Recently, vitamin D3 was found to directly influence skin dendritic cells to drive Th2 response independently of thymic stromal lymphopoietin.[80] Basophils were identified as one of the main producer of IL-4 identified in mice and are consequently a potential therapeutic target.[81] In turn, in vitro stimulation of eosinophils with IL-4 and IL-13 lead to an overexpression of the histamine-receptor H4R whose antagonists are already in clinical trials for AE.[82-84] Eosinophils, mast cells, dermal dendritic cells, natural killer cells and macrophages were found in significantly higher numbers in biopsies from lesional AE skin.[85]

The innate immune system of the skin consisting of biochemical and cellular components is the first line of defence and senses and regulates the skin microbiome.[2,86] Multiple mutations in the innate immune system pathways (eg ADAM33, MIF, MMP9, ORM2, RETN and TLR2),[53] as well as a lack of antimicrobial peptides (AMPs) were reported in the context of AE. The AMPs LL-37, human beta-defensin-2 (hBD-2) and hBD-3 are downregulated in AE skin lesions compared to psoriasis lesions.[87,88] A deficiency of antimicrobial peptides in the sweat of AE patients correlates with an impaired innate defence in AE.[89] Interestingly, AMPs are not only produced by the skin itself, but also by microbes.[90] Not only AMPs but also pattern recognition receptors like Toll-like receptors (TLRs) reveal polymorphisms and aberrant expressions in AE, among them TLR2, which is capable of sensing Gram-positive staphylococci as *S. aureus* and TLR9.[91,92] Interestingly, TLR2, which has been associated with severe forms of AE, can both lead to amplification of cutaneous inflammation and severe immunosuppression in combination with TLR6.[93] *S. aureus* strains of AE patients but not laboratory strains were reported to accumulate in keratinocytes and induce IL-1alpha via TLR9,[94] further exacerbating the inflammation. It has been shown that different staphylococcal antigens cause individual response on the specific IgG and IgA production,[95] but also interactions between IgE and staphylococcal antigens like SEA, SEB or fibronectin have been reported to play a role in disease development by activating specific IgE- and T cell–mediated immune responses.[96,97] In addition, it is also known that *S. aureus* can evade the T cell–mediated response at different steps and evades immunological memory which may have implications on vaccine development.[98]

TABLE 1 Currently available and upcoming treatment options

Systemic treatment	Target/mode of action	Stage	Efficacy to placebo	Treatment duration	Age	Common reported treatment-emergent adverse effects	Comment	Guideline recommendation
Abrocitinib	JAK–1 Inhibition	Unapproved, 2 RCT	Superior to placebo (EASI, IGA)	12 weeks	>12 years, adults	Pneumonia, eczema herpeticatum, herpes simplex infections, gastrointestinal complaints, thrombocytopenia		No statement
Apremilast	PDE–4-Inhibition	Unapproved, 1 RCT	Superior to placebo (EASI, DLQI)	12 weeks	Adults	Cellulitis	Already approved for psoriasis, psoriasis arthritis, Behcet's disease	Not recommended
Azathioprine	Inhibition of purine synthesis	Unapproved, 3 RCT	Superior to placebo (SASSAD, pruritus/ sleep disturbance VAS, DLQI)	12 weeks – 5 years	>16 years, adults	Myelosuppression, hepatotoxicity, gastrointestinal adverse effects, infections, headache	Disease-modifying drug in auto-immune diseases	May be considered as off-label use for refractory and severe cases of AD after exhaustion or drop-out of other treatment options (dupilumab, ciclosporin)
Baricitinib	JAK–1/ JAK–2-Inhibition	Approved	Superior to placebo (EASI, SCORAD,IGA; DLQI, POEM, NRS itch)	16 weeks	Adults	Nasopharyngitis / polyps, upper respiratory tract inflammation, elevation of creatine phosphokinase levels, headache	Already approved for rheumatoid arthritis	Not yet
Cyclosporine A	Calcineurin-Inhibition	Approved	Superior to placebo in nonvalidated and validated scores (EDI, pruritus/sleep loss VAS, SASSAD, UKSIP)	6–52 weeks	>7 years, adults	Nephrotoxicity, hypertension, gastrointestinal adverse effects, headache, hypertrichosis, upper respiratory tract infection	Prevention of graft-versus-host disease, prevention of rejection of transplants	May be considered for short to medium-term treatment in children (off-label), adolescents and adults with refractory and severe AD

(Continues)

TABLE 1 (Continued)

Systemic treatment	Target/mode of action	Stage	Efficacy to placebo	Treatment duration	Age	Common reported treatment-emergent adverse effects	Comment	Guideline recommendation
Corticosteroids (prednisolone, beclomethasone, flunisolide)	Interaction with the glucocorticoid receptor (genomic, non-genomic)	Unapproved, 85 RCT	Superior to placebo in nonvalidated scores,	4–52 weeks	Children, adults	Exacerbations of eczema	Allergic reactions among others	Due to long term adverse effects only for short term treatment in severe cases of paediatric or adult AD
Dupilumab	Inhibition of IL–4Ra: blockade of IL–4/ IL–13-signalling	Approved	Superior to placebo (EASI, IGA, NRS itch, POEM, DLQI, cDLQI, GISS, QoLIAD)	4–76 weeks	Children, adults	Conjunctivitis, injection site reactions, upper respiratory infection, nasopharyngitis, headache, herpes simplex infection	Also approved for asthma, chronic sinusitis with nasal polyposis	May be recommended for children (>6 years) / adults with chronic and severe / chronic and moderate to severe AD
Lebrikizumab	Binding of IL–13: Blockade of IL–13 signalling	Unapproved	Superior to placebo (EASI, IGA)	12–16 weeks	Adults	No serious or dose-dependent TEAE		No statement
Mepolizumab	IL–5-Inhibition	Unapproved, 1 RCT	Not superior to placebo (SCORAD, VAS pruritus)	4 weeks	Adults	Not reported	Approved for severe eosinophilic asthma and eosinophilic granulomatosis with polyangiitis	
Methotrexate	Antimetabolite (antifolate): inhibition of DNA, RNA, thymidylate and protein synthesis	Unapproved, 3 RCT	No trials with comparison to placebo; superior to azathioprine (SCORAD), cyclosporine (SCORAD)	12 weeks - 5 years	Children, adults	Hepatitis, gastrointestinal side effects	Disease-modifying drug in auto-immune diseases, chemotherapy	May be considered as a off-label use for chronic and severe cases of AD.
Nemolizumab	Binding of IL–31-receptor-alpha-unit	Unapproved, 2 RCT	Superior to placebo (EASI, IGA, NRS)	24–64 weeks	Adults	Nasopharyngitis, upper respiratory tract infection		No statement
Omalizumab	Depletion of IgE	Unapproved, 2 RCT	Conflicting results: superiority (EASI, SCORAD, DLQI); non-superiority (EASI, SCORAD, IGA)	16–24 weeks	Children, adults	Abdominal pain, nausea, allergic reactions, exacerbation of eczema	Approved for chronic urticaria, asthma	Not recommended

(Continues)

TABLE 1 (Continued)

Systemic treatment	Target/mode of action	Stage	Efficacy to placebo	Treatment duration	Age	Common reported treatment-emergent adverse effects	Comment	Guideline recommendation
Tralokinumab	Binding of IL–13: Blockade of IL–13 signalling and regulation	Unapproved, 3 RCT	Superior to placebo (EASI)	12 weeks	Adults	Headache, upper respiratory tract infection		No statement
Upadacitinib	JAK–1-Inhibition	Unapproved, 1 RCT	Superior to placebo (EASI, SCORAD, NRS itch)	16 weeks	Adults	Upper respiratory tract infection, exacerbation of AD, acne, arrhythmia, dental disease, appendicitis	Approved for rheumatoid arthritis	No statement
Ustekinumab	Il–12-/IL–23p40-antagonist	Unapproved, 2 RCT	Non-superiority to placebo (EASI, SCORAD, DLQI, ADIS)	12–24 weeks	Adults	Nasopharyngitis, contact dermatitis, eczema herpeticatum	Approved for psoriasis, psoriasis arthritis, Crohn's disease, ulcerative colitis	Treatment with ustekinumab may be considered in cases of coincidence of AD with psoriasis, psoriasis arthritis, rheumatoid arthritis or chronic inflammatory bowel disease
Topical treatment								
Crisaborole	PDE4B Inhibition	Approved (US)	Superior to vehicle (ISGA)	4 weeks	>2 years, adults	Application site stinging/burning/pain	Suitable as a steroid-sparing agent, but questionable cost-effectiveness	No statement
Ruxolitinib	JAK–1/JAK–2-Inhibition	Unapproved	Superior to vehicle (EASI, IGA, NRS itch)	4 weeks	Adults	Studies for children are underway		No statement

Note: Data are showing topical and systemic treatment options adapted from previous literature.[117,135-138]

Abbreviations: SASSAD, Six area; six sign atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment; ISGA, Investigator's Static Global Assessment; (c)DLQI, (Children's) Dermatology Life Qualitiy Index; VAS, Visual Analogue Scale; SCORAD, SCOring Atopic Dermatitis; NRS, Numeric Rating Scale; EDI, Eczema Disability Index; POEM, Patient Oriented Eczema Measure; GISS, Global Individual Sign Score; QoLIAD, Quality of Life Index for Atopic Dermatitis; ADIS, Atopic Dermatitis Itch Scale; TEAE, Treatment-Emergent Adverse Events.

5 | DIAGNOSIS AND CLINICAL ASSESSMENT OF SEVERITY

The American Academy of Dermatology (AAD) developed consensus criteria for clinicians for the diagnosis of AE especially in young children consisting of three sub-categories of essential, important and associated features.[99] Novel biomarkers to distinguish early in life between AE and hyper IgE syndrome (HIES) were recently reported, specifically, an upregulation of CXCL10 and TNF-α and a downregulation of EGF for HIES compared to AE patients.[100] AE severity (from mild to severe) can be elucidated by validated scores like Scoring atopic dermatitis (SCORAD) or Eczema Area and Severity Index (EASI) which are useful for clinical trials.[101] For daily assessment of treatment success, the novel and quick to fill atopic dermatitis score 7 (ADS7) has been proposed, which considers lesions and discomfort as itch and quality of life.[102]

6 | BIOMARKERS FOR DISEASE SEVERITY

Multiple factors have been described to correlate with AE severity. Measurement of NMFs via Raman spectroscopy has been shown to be a reliable clinical marker for AE and can be used when deciding for treatment.[103] To objectively measure skin integrity, electrical impedance spectroscopy (EIS) measurements can be performed.[104] EIS measurements could be used to distinguish between healthy, AE non-lesional and lesional skin, correlated positively with disease severity, and correlated inversely with biomarkers associated with inflammation, making it a more reliable and sensitive tool for in vivo barrier disruption detection than transepidermal waterloss (TEWL) measurements.[105] Also, the microbiome can be used as a marker for disease severity, assess risk-prone state of skin, and predict treatment response in children across human populations.[106] Among them are bacterial factors as *S. aureus* abundance, which has been correlated with disease severity, but also as a biomarker for disease worsening.[67,107] However, before the skin microbiome can be widely used as clinical biomarker, a standardized method would be required for microbiome analysis.[108] Also immunological factors are associated with disease severity, for example thymus and activation-regulated chemokine (TARC) detected in dried blood spots.[109] A biomarker signature (p-EASI) based on multiple immunological biomarkers reliably predicts disease severity.[110,111] Local, non-invasive sampling of the skin would be well-tolerated and allows a thorough analysis of the complex interplay of the skin barrier, the immune system and microbes in vivo. Allergy-associated genes and gene-variants are now listed in the database *AllergyGenDB* which thus can be used for hypothesis generation in research.[112] Thorough endotyping of AE patients would be very efficient and cost-effective for treatment.[113] One possible method would be tape stripping, which successfully revealed multiple AE markers in a current study.[114] Biomarkers are essential for diagnosis and personalized and tailored therapy, especially in a multifaceted disease as AE.[115]

7 | THERAPY

AE therapy has undergone a true revolution in recent years. We are on the way to being spoilt for choice in deciding which systemic therapy to use. What remains to be seen, however, is which subtype of AE will respond to which new targeted drug. Tailored treatment strategy in AE depends on the individual patients' age, history and disease severity, evaluated by assessing both objective and subjective factors.[116,117] Interestingly, unique T-cell subsets and cytokine patterns in paediatric compared to adult AE patients urge for age-specific therapies.[116,118] Considering the multidimensional nature of AE, effective disease management incorporates different pillars of treatment. Besides basic skin care and individual pharmacological approaches, patient education and self-management strategies that address social and environmental factors have to be included—not only to optimize individual outcomes, but also to reduce unnecessary costs associated with the management of AE.[119] The knowledge and therapy options expand rapidly in AE and the current standards for diagnosis and therapy are nicely summarized by Wollenberg et al.[120] Interestingly, a recent study has shown that patients self-reported disease severity seems to be correlated with treatment satisfaction of AE patients.[121]

7.1 | Local therapy

With respect to the skin barrier dysfunction as a pathognomonic factor in the pathogenesis of AE, emollient therapy marks an essential element in the disease management: Application of emollients in adequate amount (>250g/week) and frequency (at least once, better twice a day; additionally, after any skin cleansing) is necessary to enhance the integrity of epidermal barrier and consequently reduce the susceptibility for irritation and inflammation of the skin. Interestingly, a pilot study has recently shown greater efficacy of a novel trilipid cream (a 3:1:1 ratio of ceramides, cholesterol and free fatty acids) than a regular paraffin-based emollient considering the reduction of transepidermal water loss.[122]

Topical anti-inflammatory treatment is still the mainstay of mild-to-moderate forms of AE and especially acute exacerbations due to a reduction of pruritus and inflammation and restoration of skin barrier function. Both topical corticosteroids (TCS) and calcineurin inhibitors (TCI) have shown to be safe and effective for reducing acute flares and risk of relapse if applied in an appropriate intensity and dosage, especially in a proactive setting (eg twice weekly usage on predilection areas). Concomitant use of emollients in an appropriate amount has proved a steroid-sparing effect.[123,124] Besides their anti-inflammatory properties, positive cutaneous microbiome effects have been shown for TCS and TCI.

Promising new topical agents that inhibit key regulators of pro-inflammatory signals are in clinical development (eg Janus Kinase Inhibitors) or have been recently approved (eg selective Phosphodiesterase 4 Inhibitor Crisaborole) (see Table 1). Further

real-life studies will have to show their potential role in management of AE.[120]

In many cases, adequate control of AE can be achieved by topical treatment options, if applicable even in combination with phototherapy (eg UVB and UVA-1). However, if local therapy remains insufficient, or in case of severe or persistent disease, systemic treatment is indicated.

7.2 | Skin barrier as a potential target for treatment—new developments

The disturbed skin barrier offers a variety of novel leverage points for future AE treatment. One option would be to tackle the dysbalanced skin microbiome with pre- and probiotics. A study achieved positive results by applying heat-treated *Lactobacillus johnsonii* NCC 533 on AE skin.[125] The topical microbiome transplant of *Roseomonas mucosa* from healthy participants to AE patients improved AE severity in a clinical I/II safety and activity trial.[126] As *S. aureus* is one of the driving factors in AE, multiple strategies to control *S. aureus* growth emerged. An active reduction of *S. aureus* could be achieved with competing coagulase-negative staphylococci (CoNS) which produce antimicrobial peptides against *S. aureus*.[127] Furthermore, it could be shown that CoNS could inhibit quorum sensing and thereby virulence of *S. aureus*.[128,129] Another strategy is to shift the microenvironment towards unfavourable conditions for *S. aureus*. As acidic and alkaline pH seem to limit the growth of *S. aureus* in vitro and in vivo, acidification of the skin could be one strategy. However, sustained acidification of the skin was not yet successful.[67,130] Therefore, more acidic products, well-buffered products or a more continuous application of the emollient could be beneficial. Dilute bleach baths also do not reduce *S. aureus* load and AE severity in vivo or in vitro.[67,101,130,131] Contrastingly, removal of *S. aureus* by UVB is known to be quite successful.[132] An exciting new strategy in AE management could also be an anti-*S. aureus* vaccine.[133]

7.3 | Systemic therapy

For severe forms of AD or cases that do not respond adequately to topical treatment, systemic therapy should be considered. In practice, several systemic anti-inflammatory treatment options are established for treating AE: Until approval of dupilumab in 2017 and baricitinib in 2020, cyclosporine has been considered as first-line option over many years. Other immunosuppressive drugs (eg azathioprine, methotrexate) have been also used with good response, but off label and/or as second-line therapy, in AE.[134,135] As stated above, many different cellular and molecular effectors are involved in AE. The expanding knowledge of this complex type 2 immunological background of AE leads to new developments of new cytokine-directed treatment options that are currently under investigation (Table 1).[117,135-138]

The European Academy of Allergy and Clinical Immunology (EAACI) AE guideline group nicely summarized evidence on systemic treatments for AE identifying the need for trials comparing novel systemic treatments with conventional therapies.[135]

Besides skin inflammation and barrier dysfunction, itch represents a cardinal symptom of AE. For a long time, histamine has been assumed to be the main mediator of itch. Antihistamines have been commonly used for reducing itch in AE patients, but with conflicting evidence. Two Cochrane studies have recently shown that antihistamines have no or just a limited antipruritic effect.[139,140] It is important to note that recent research has resulted in progress in understanding the complex pathophysiology of atopic itch, from which more specific treatment options will arise perspectively.[141]

7.4 | New developments in systemic treatment options

Several more biologics and small molecules interfering with key mediators of AE are currently in development and may contribute to tailored therapeutic approaches in future.[78] An interesting approach to improve AE in patients unresponsive to extensive therapy is, to use repetitive transient reductions of total IgE, which lead in a small number of patients to long-lasting improvement of AE with improvement of both clinical parameters as well as the quality of life.[142] Allergen-specific immunotherapy (ASIT) is currently not recommended as a common treatment approach.[132] But ASIT against animal dander has been shown to reduce specific IgE in AE patients and could be effective treatment option for patients with respiratory allergic comorbidities.[143] Additionally, downregulatory strategies for the immune system are under investigation. CD300a expression has a downregulatory role in AE (mice), this could be an anti-inflammatory strategy.[85] The immune system in epithelial cells is posttranscriptional regulated by miRNAs.[144] Among others, miR-10a-5p has been identified to modulate AE targets.[145] L-type amino acid transporter 1 (LAT1) is critical for activating human and mouse T cells and its inhibition reveals a potential new target for AE treatment.[146]

It is important to increase the knowledge about the complex mechanisms influencing AE and therefore a combination of patient information correlated with biomaterial analysis and in vitro testing is needed. The CK-CARE program will contribute to identify and validate new and reliable biomarkers for precision medicine.[147]

8 | PREVENTION

As the underlying skin barrier defects observed in AE are the first step in the atopic march, the prevention of AE is very appealing—and especially in families with known risk factors—highly important. As emollients are the primary management strategy in AE, emollient application at early age is an obvious prevention method for AE. Contradictory data exist on its efficiency. Whereas earlier studies hinted towards a highly effective approach for AE prevention in neonates, this could not be confirmed in recent studies where no

evidence was found that daily emollients had a preventive effect in neither a population-based nor a high-risk cohort.[148-153] One factor for the conflicting results could be the formulation of the ointment. Ceramide-based emollients are more efficient in reducing the TEWL, whereas peanut-oil based ointments were reported to be a facilitator for allergy.[122,154] Due to the barrier defect, emollient components can most likely cross the skin barrier more easily in AE. Even though early supplementation of peanut, cow milk, wheat and eggs was not protective for AE,[149] a diverse diet and cheese consumption seem to be beneficial, possibly due to the high microbial diversity found in cheese.[155,156] In the same direction, pre- and probiotics are potentially protective for AE development.[157] Although prebiotics are non-digestional ingredients which promote beneficial bacteria such as Bifidobacterium and Lactobacilli, probiotics are active bacteria which are beneficial for human health.[158,159] Among them are *Bifidobacterium* and *Lactobacilli*, Gram-positive, anaerobic bacteria which are potentially capable of producing lactic-acids and antimicrobial substances and bacteriocins, limiting potentially pathogenic gut bacteria.[157] The data on the efficiency of pre- and probiotics are highly controversial, likely due to differences in type or mixture of strains.[160] Orally applied prebiotic *Escherichia coli* and *Enterococcus faecalis* in children were ineffective in AE prevention.[161] Contrarily, the administration of probiotics during pregnancy has been confirmed to prevent AE of the children in a meta-analysis of 19 studies.[162] Continuation of probiotics during breastfeeding and then the infant seemed efficient in reducing the risk of AE.[160,163]

9 | HOT TOPIC—ATOPIC ECZEMA AND SARS-COV-2

In the context of the Corona pandemic, it is of interest that especially one known SARS-CoV-2 receptor, CD147 and its related molecules, are expressed higher in lesions of AE patients than healthy controls and could hint towards a predisposition towards SARS-CoV-2 infections.[164] However, allergy was not identified as risk factor for bad COVID-19 outcome in children.[165] Therefore, it is advised for AE patients to continue immune-modulating treatments.[166,167] Also, COVID-19 vaccinations are recommended for AE patients without pausing medication before or after vaccination.[168]

10 | CONCLUSION

Atopic dermatitis is a complex skin disease with underlying skin barrier defects. Multiple intrinsic but also extrinsic factors put humans at risk to develop AE—among them environmental factors which in times of climate change could play an even stronger role in future. However, the heterogenous disease can be divided into multiple endotypes with different pathomechanisms. Therefore, a personalized medicine approach for an effective management of AE is needed. New strategies emerged in the last years, tackling the skin barrier including the microbiome or factors of the immune system. Even better would be the prevention of AE, possibly by suitable emollients or pre- and probiotics, as AE is known and confirmed to be the first step of the atopic march. Many parts of the complex disease mechanisms could be unravelled in the last decades. However, much is still unknown and must be addressed by the science community, particularly host-microbe and environmental interaction.

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CONFLICT OF INTEREST

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ORCID

Claudia Hülpüsch https://orcid.org/0000-0002-5711-1356
Andreas B. Weins https://orcid.org/0000-0002-0982-7122
Claudia Traidl-Hoffmann https://orcid.org/0000-0001-5085-5179
Matthias Reiger https://orcid.org/0000-0002-6173-2104

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