

Title: A new era of atopic eczema research: Advances and highlights

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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 is 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 the 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.

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 presentation defined by the ethnicity, disease onset, disease severity, chronic vs acute, intrinsic vs extrinsic (IgE level), pediatric 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 socioeconomic 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", i.e. begin a classic "allergy career". Scientifically, atopic dermatitis 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. AE 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 [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, 27] [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, cesarean 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]. The patient’s residence also determines the exposure to air-pollutants which are associated with AE development. One major component of environmental air pollutants are Diesel exhaust particles, which triggers an itch-scratch response by binding to the aryl hydrocarbon receptor AhR [37, 38] [39]. Children seem to be more vulnerable than adults to pollution as an AE exacerbation trigger [40]. 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 [41, 42]. In line, psychological interventions had a positive effect on AE severity in a meta-analysis and were also associated with other allergic diseases [43, 44].

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 serum CEGF levels at three years [4] as well as by early onset and high IL-13 levels [45] [46]. Furthermore, the risk to develop allergic rhinitis – especially in untreated AE - [46] or adult onset-asthma is significantly higher in patients with allergic diseases and AE [47]. Therefore, AE is claimed to be the first step of the so-called atopic march [48]. 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 identifies multimorbidity for asthma, rhinitis, and dermatitis [49]. 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 (e.g. FLG, COL5A3, COL6A6, and MMP9, TMEM79) [50, 51]. A variety of AE mice models are used to investigate skin barrier defects, among them FLG *ft/ft* mice [52], *Hrnr*^{-/-} mice [53], and *TMEM79*^{-/-} mice [51]. One major genetic predisposition for the development of AE are loss-of-function mutations in the skin barrier gene filaggrin [54]. Degradation products of histidine-rich filaggrin support the healthy skin barrier as natural moisturizing factors (NMF) and simultaneously maintain an acidic skin pH [55]. The skin pH in AE and especially AE lesions was reported to be increased [56]. 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 [57, 58]. 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 [59]. 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 [60]. 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 [61, 62].

A skin microbiome dysbiosis towards *Staphylococcus aureus* and decreased microbial diversity is another hallmark of AE [63]. 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* [64, 65]. Genetics also shape the skin microbiome as recently shown in a mouse model: wild-type and Flgft/ft mice significantly differed in the skin microbiome composition, revealing less diversity with an increased staphylococci colonization [52]. In this study, AE did not develop under germ free conditions but was dependent on microbial colonization and subsequent IL-1beta induction [52]. 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 [66]. Not only the presence of *S. aureus* but also capability of *S. aureus* strains to produce biofilm and toxins is associated with AE severity [63, 67] [67, 68]. *S. aureus* activates the immune system in AE amongst others by the expression of proteases, toxins, superantigens and other virulence factors [63, 69] (Fig. 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, 70]. 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 [63].

In the context of itch and scratch-response, sensory neurons are important [71]. However, the nervous system is not only responsible for pruritus, but also modulates the immune response in AE [72].

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 e.g. 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 down regulation of fil-aggrin and claudins and recruitment of eosinophils [73-75] [76]. Recently, vitamin D3 was found to induce skin dendritic cells to differentiate Th2 cells [77]. Basophils were identified as one of the main producer of IL-4 identified in mice and is consequently a potential therapeutic target [78]. 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 [79, 80] [81]. Eosinophils, mast cells, dermal dendritic cells, natural killer cells, and macrophages, were found in significantly higher numbers in biopsies from lesional AE skin [82].

The innate immune system of the skin consisting of biochemical and cellular components is the first line of defense and senses and regulates the skin microbiome. [2, 83] Multiple mutations in the innate immune system pathways (e.g. ADAM33, MIF, MMP9, ORM2, RETN, and TLR2) [50], as well as a lack of antimicrobial peptides (AMPs) were reported in the context of AE. The AMPs LL-37, hBD-2, and hBD-3 are downregulated in AE skin lesions compared to psoriasis lesions [84, 85]. A deficiency of antimicrobial peptides in the sweat of AE patients correlate with an impaired innate defense in AE [86]. Interestingly, AMPs are not only produced by the skin itself, but also by microbes [87]. 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 TLR-9. [88] [89]. 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 [90]. *S. aureus* strains

of AE patients but not laboratory strains were reported to accumulate in keratinocytes and induce IL-1alpha via TLR9 [91], further exacerbating the inflammation.

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 [92]. Novel biomarkers to distinguish early in life between AE and HIES were recently reported, specifically an upregulation of CXCL10 and TNF-A and a downregulation of EGF for HIES compared to AE patients [93]. To objectively measure skin integrity, electrical impedance measurements can be performed [94]. AE severity (from mild to severe) can be elucidated by validated scores like SCORAD or EASI which are useful for clinical trials [95]. For daily assessment of treatment success, the novel and quick to fill score ASD7 has been proposed, which considers lesions and discomfort as itch and quality of life [96].

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 [97]. 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 [98]. Among them are bacterial factors as *S. aureus* abundance, which has been correlated with disease severity, but also as a biomarker for disease worsening [64, 99]. However, before the skin microbiome it can be widely used as clinical biomarker, a standardized method would be required for microbiome analysis [100]. Also immunological factors are associated with disease severity, e.g. TARC detected in dried blood spots [101]. A biomarker signature (p-EASI) based on multiple immunological biomarkers reliably predicts disease severity, [102, 103]. 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 [104]. Thorough endotyping of AE patients would be very efficient and cost-effective for treatment [105]. One possible method would be tape stripping, which successfully revealed multiple AE markers in a current study [106]. Biomarkers are essential for diagnosis and personalized and tailored therapy, especially in a multifaceted disease as AE [107].

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 [108, 109]. Interestingly, unique T-cell subsets and cytokine patterns in pediatric compared to adult AE patients urge for age-specific therapies [110] [108]. 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 [111]. The knowledge and therapy options expand rapidly in AE and the current standards for diagnosis and therapy are nicely summarized by Wollenberg et al [112, 113]. Interestingly, a recent study has shown that patients self-reported disease severity seems to be correlated with treatment satisfaction of AE patients [114].

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 [115].

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 (e.g. twice weekly usage on predilection areas). Concomitant use of emollients in an appropriate amount has proved a steroid-sparing effect [116, 117]. 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 (e.g. topical Janus Kinase Inhibitors) or have been recently approved (topical selective phosphodiesterase 4 inhibitor Crisaborole). Further studies will have to show their potential role in management of AE [112].

In many cases, adequate control of AE can be achieved by topical treatment options, if applicable even in combination with phototherapy (e.g. UVB, 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 [118]. 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 [119]. As *S. aureus* 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* [120]. Furthermore, it could be shown that CoNS could inhibit quorum sensing and thereby virulence of *S. aureus* [121, 122]. Another strategy is to shift the microenvironment towards unfavorable conditions for *S. aureus*. As acidic and alkaline pH seems 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 [64, 123]. 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 [64, 95, 123, 124]. Contrastingly, removal of *S. aureus* by UVB is known to be quite successful [125]. An exciting new strategy in AE management could also be an anti-*S. aureus* vaccine [126].

7.3 Systemic therapy

In practice, several systemic 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 drugs (e.g. azathioprine, methotrexate and mycophenolic acid) have been also used with good response, but off label and/or as second line therapy, in AE [113, 127]. 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 [128].

Dupilumab

A very effective biologic for AE treatment seems to be dupilumab [75], a human monoclonal antibody that binds IL-4R α thereby blocking type 2 inflammation and restoring epidermal barrier [129, 130]. It has been shown that dupilumab improves symptoms and severity of disease, as well as AE-related serum biomarkers even in a subset of very difficult-to-treat AE patients [131]. Dupilumab has been recently approved as the first biologic treatment for children with moderate and severe AE. Albeit current data suggest no harmful effects of dupilumab on animal fetus, possible risks associated with exposure of the biologic during pregnancy in women

have to be still further investigated [132]. Overall, the acceptance of the biologic agent seems high as reflected in the very long drug survival or compliance time of the patients [133]. This is strongly connected with the benefit of improving symptoms and disease severity, reducing the use of rescue medications and improving the quality of life and in parallel with a low risk for adverse events [134, 135]. Ocular (conjunctivitis) and local reactions have been reported as the major adverse effects in dupilumab-treated patients [127]. Dupilumab has also proved efficacy in a study with another systemic Th2 disease, chronic rhinosinusitis with nasal polyposis: Treatment with the antibody resulted in reduction of multiple biomarkers of type 2 inflammation in nasal secretions and polyp tissues [136], but also perennial allergic rhinoconjunctivitis and perennial allergic asthma symptoms [137].

Baricitinib

The spectrum of systemic treatment options in AE has recently expanded by approval of baricitinib, an oral JAK inhibitor. The small molecule has been proved efficacy and safety in several RCTs with an improvement of itch, patient-oriented eczema measure and DLQI [127].

7.4 New developments in systemic treatment options

Many different cellular and molecular effectors are involved in AE. A recent review summarizes important players in type 2 immunity in regards to AE and Asthma [138]. The expanding knowledge of this complex type 2 immunological background of AE led to new developments of new cytokine-directed treatment options that are currently under investigation: Mepolizumab (anti-IL-5) treatment did not show an clinical improvement of AE patients in short and longterm phase-2 clinical trial [139]. Antibodies interfering with IL-13 (lebrikizumab, tralokinumab) have shown promising results in ongoing studies, while selective neutralization of IL-31 (nemolizumab) proved efficacy in reducing itch, but only moderate EASI response [75]. 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 [75]. 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 [140]. Additionally, downregulatory strategies for the immune system are under investigation. CD300a expression has a downregulatory role in AE (mice), thus could be an anti-inflammatory strategy [82]. The immune system in epithelial cells is posttranscriptional regulated by miRNAs [141]. Amongst others, miR-10a-5p has been identified to modulate AE targets [142]. 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 [143].

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 [144].

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 exists 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 [145-150]. 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 [115, 151]. 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 [146], a diverse diet and cheese consumption seem to be beneficial, possibly due to the high microbial diversity found in cheese [152, 153]. In the same direction, pre- and probiotics

are potentially protective for AE development [154]. Whereas prebiotics are non-digestional ingredients which promote beneficial bacteria such as Bifidobacterium and Lactobacilli, probiotics are active bacteria which are beneficial for human health [155, 156]. 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 [154]. The data on the efficiency of pre- and probiotics is highly controversial, likely due to differences in type or mixture of strains [157]. Orally applied prebiotic *Escherichia coli* and *Enterococcus faecalis* in children were ineffective in AE prevention [158]. Contrarily, the administration of probiotics during pregnancy has been confirmed to prevent AE of the children in a meta-analysis of 19 studies [159]. Continuation of probiotics during breastfeeding and then the infant seemed efficient in reducing the risk of AE [157, 160].

9. 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 the 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. 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. Much of the complex disease mechanisms could be unraveled in the last decades. However, much is still unknown and must be addressed by the science community, particularly host-microbe and environmental interaction.

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 e.g. 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 (e.g. pH) and the immune system (e.g. Vitamin D3, sport, food) should be in focus
- Time frame and trigger factors for AE development must be further investigated

Conflict of Interest

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Author contributions

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1. Eyerich, S., et al., *Cutaneous Barriers and Skin Immunity: Differentiating A Connected Network*. Trends Immunol, 2018.**39** (4): p. 315-327.
2. Werfel, T., et al., *Cellular and molecular immunologic mechanisms in patients with atopic dermatitis*. J Allergy Clin Immunol, 2016. **138** (2): p. 336-49.
3. Bieber, T., et al., *Clinical phenotypes and endophenotypes of atopic dermatitis: Where are we, and where should we go?* J Allergy Clin Immunol, 2017. **139** (4s): p. S58-s64.
4. Lauffer, F., et al., *Predicting persistence of atopic dermatitis in children using clinical attributes and serum proteins*. Allergy, 2020.
5. Czarnowicki, T., et al., *Atopic dermatitis endotypes and implications for targeted therapeutics*. J Allergy Clin Immunol, 2019.**143** (1): p. 1-11.
6. Zeiser, K., et al., *Social and psychosocial effects on atopic eczema symptom severity – a scoping review of observational studies published from 1989 to 2019*. Journal of the European Academy of Dermatology and Venereology, 2021. **35** (4): p. 835-843.
7. Barbarot, S., et al., *Epidemiology of atopic dermatitis in adults: Results from an international survey*. Allergy, 2018.**73** (6): p. 1284-1293.
8. Kowalska-Oledzka, E., M. Czarnecka, and A. Baran, *Epidemiology of atopic dermatitis in Europe*. J Drug Assess, 2019. **8** (1): p. 126-128.
9. Cork, M.J., S.G. Danby, and G.S. Ogg, *Atopic dermatitis epidemiology and unmet need in the United Kingdom*. J Dermatolog Treat, 2020. **31** (8): p. 801-809.
10. Drucker, A.M., et al., *The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association*. J Invest Dermatol, 2017. **137** (1): p. 26-30.
11. Silverberg, J.I., *Public Health Burden and Epidemiology of Atopic Dermatitis*. Dermatol Clin, 2017. **35** (3): p. 283-289.
12. Sasaki, M., et al., *The change in the prevalence of wheeze, eczema and rhino-conjunctivitis among Japanese children: Findings from 3 nationwide cross-sectional surveys between 2005 and 2015*. Allergy, 2019. **74** (8): p. 1572-1575.
13. Paller, A.S., et al., *The atopic march and atopic multimorbidity: Many trajectories, many pathways*. J Allergy Clin Immunol, 2019. **143** (1): p. 46-55.
14. Zuberbier, T., et al., *Economic burden of inadequate management of allergic diseases in the European Union: a GA(2) LEN review*. Allergy, 2014. **69** (10): p. 1275-9.
15. Bylund, S., et al., *Prevalence and Incidence of Atopic Dermatitis: A Systematic Review*. Acta Derm Venereol, 2020.**100** (12): p. adv00160.
16. Kantor, R. and J.I. Silverberg, *Environmental risk factors and their role in the management of atopic dermatitis*. Expert Rev Clin Immunol, 2017. **13** (1): p. 15-26.
17. Traidl-Hoffmann, C., *[Allergy - an environmental disease]*. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 2017. **60** (6): p. 584-591.
18. Gilles, S., et al., *The role of environmental factors in allergy: A critical reappraisal*. Experimental Dermatology, 2018.**27** (11): p. 1193-1200.
19. Heuson, C. and C. Traidl-Hoffmann, *[The significance of climate and environment protection for health under special consideration of skin barrier damages and allergic sequelae]*. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz, 2018.**61** (6): p. 684-696.

20. Alkotob, S.S., et al., *Advances and novel developments in environmental influences on the development of atopic diseases*. Allergy, 2020. **75** (12): p. 3077-3086.
21. Hale, G., et al., *What's new in atopic eczema? An analysis of systematic reviews published in 2017. Part 2: epidemiology, aetiology and risk factors*. Clin Exp Dermatol, 2019. **44** (8): p. 868-873.
22. Boutin, R.C.T., et al., *Mining the infant gut microbiota for therapeutic targets against atopic disease*. Allergy, 2020. **75** (8): p. 2065-2068.
23. Venter, C., et al., *EAAACI position paper: Influence of dietary fatty acids on asthma, food allergy, and atopic dermatitis*. Allergy, 2019. **74** (8): p. 1429-1444.
24. Chang, Y.S., et al., *Association between keratoconus and the risk of adolescent- or adult-onset atopic dermatitis*. Allergy, 2020. **75** (11): p. 2946-2948.
25. Kantor, R., et al., *Association of atopic dermatitis with smoking: A systematic review and meta-analysis*. Journal of the American Academy of Dermatology, 2016. **75** (6): p. 1119-1125.e1.
26. Haahtela, T., et al., *The biodiversity hypothesis and allergic disease: world allergy organization position statement*. World Allergy Organ J, 2013. **6** (1): p. 3.
27. Haahtela, T., *A biodiversity hypothesis*. Allergy, 2019. **74** (8): p. 1445-1456.
28. Rook, G.A.W., *A Darwinian View of the Hygiene or "Old Friends" Hypothesis*. Microbe Magazine, 2012. **7** (4): p. 173-180.
29. Walter, J. and L. O'Mahony, *The importance of social networks—An ecological and evolutionary framework to explain the role of microbes in the aetiology of allergy and asthma*. Allergy, 2019. **74** (11): p. 2248-2251.
30. Xu, F., et al., *Prevalence of childhood atopic dermatitis: an urban and rural community-based study in Shanghai, China*. PloS one, 2012. **7** (5): p. e36174-e36174.
31. Chatenoud, L., et al., *Markers of microbial exposure lower the incidence of atopic dermatitis*. Allergy, 2020. **75** (1): p. 104-115.
32. Thyssen, J.P., et al., *Interaction between filaggrin mutations and neonatal cat exposure in atopic dermatitis*. Allergy, 2020. **75** (6): p. 1481-1485.
33. Marrs, T., et al., *Dog ownership at three months of age is associated with protection against food allergy*. Allergy, 2019. **74** (11): p. 2212-2219.
34. Skajaa, N., et al., *Cesarean delivery and risk of atopic dermatitis*. Allergy, 2020. **75** (5): p. 1229-1231.
35. Dimitriu, P.A., et al., *New Insights into the Intrinsic and Extrinsic Factors That Shape the Human Skin Microbiome*. mBio, 2019. **10** (4).
36. Fairweather, V., E. Hertig, and C. Traidl-Hoffmann, *A brief introduction to climate change and health*. Allergy, 2020. **75** (9): p. 2352-2354.
37. Hassoun, Y., C. James, and D.I. Bernstein, *The Effects of Air Pollution on the Development of Atopic Disease*. Clin Rev Allergy Immunol, 2019. **57** (3): p. 403-414.
38. Ahn, K., *The role of air pollutants in atopic dermatitis*. Journal of Allergy and Clinical Immunology, 2014. **134** (5): p. 993-999.
39. Kabashima, K., A. Otsuka, and T. Nomura, *Linking air pollution to atopic dermatitis*. Nature Immunology, 2017. **18** (1): p. 5-6.
40. Wang, H.L., et al., *Association between air pollution and atopic dermatitis in Guangzhou, China: modification by age and season*. British Journal of Dermatology, 2020. **n/a** (n/a).
41. Raap, U. and G. Schmid-Ott, *Psychological Factors of Atopic Dermatitis* .

42. Raap, U., et al., [*Atopic dermatitis and psychological stress*]. *Hautarzt*, 2003. **54** (10): p. 925-9.
43. Chida, Y., et al., *The effects of psychological intervention on atopic dermatitis. A systematic review and meta-analysis*. *Int Arch Allergy Immunol*, 2007. **144** (1): p. 1-9.
44. Harter, K., et al., *Different Psychosocial Factors Are Associated with Seasonal and Perennial Allergies in Adults: Cross-Sectional Results of the KORA FF4 Study*. *Int Arch Allergy Immunol*, 2019. **179** (4): p. 262-272.
45. Lee, E., et al., *Atopic dermatitis phenotype with early onset and high serum IL-13 is linked to the new development of bronchial hyperresponsiveness in school children*. *Allergy*, 2016. **71** (5): p. 692-700.
46. Mortz, C.G., et al., *Atopic diseases and type I sensitization from adolescence to adulthood in an unselected population (TOACS) with focus on predictors for allergic rhinitis*. *Allergy*, 2019. **74** (2): p. 308-317.
47. Toppila-Salmi, S., et al., *Risk of adult-onset asthma increases with the number of allergic multimorbidities and decreases with age*. *Allergy*, 2019. **74** (12): p. 2406-2416.
48. Brough, H.A., et al., *Epicutaneous sensitization in the development of food allergy: What is the evidence and how can this be prevented?* *Allergy*, 2020. **75** (9): p. 2185-2205.
49. Lemonnier, N., et al., *A novel whole blood gene expression signature for asthma, dermatitis, and rhinitis multimorbidity in children and adolescents*. *Allergy*, 2020.
50. Martin, M.J., et al., *Genetics and Epigenetics of Atopic Dermatitis: An Updated Systematic Review*. *Genes*, 2020. **11** (4): p. 442.
51. Saunders, S.P., et al., *Dysregulated skin barrier function in *Tmem79* mutant mice promotes IL-17A-dependent spontaneous skin and lung inflammation*. *Allergy*, 2020.
52. Schwartz, C., et al., *Σποντανούς ατοπής δερματίτις in mice ωτη η δερματική σκιν βαρριερ ις ινδενδεντ οφ IL² ανδ μεδιατεδ βψ IL-1β*. *Allergy*, 2019. **74** (10): p. 1920-1933.
53. Rahrig, S., et al., *Transient epidermal barrier deficiency and lowered allergic threshold in filaggrin-hornerin (*FlgHmr*(-/-)) double-deficient mice*. *Allergy*, 2019. **74** (7): p. 1327-1339.
54. Palmer, C.N., et al., *Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis*. *Nat Genet*, 2006. **38** (4): p. 441-6.
55. McAleer, M.A. and A.D. Irvine, *The multifunctional role of filaggrin in allergic skin disease*. *Journal of Allergy and Clinical Immunology*, 2013. **131** (2): p. 280-291.
56. Danby, S.G. and M.J. Cork, *pH in Atopic Dermatitis* .
57. Ali, S.M. and G. Yosipovitch, *Skin pH: from basic science to basic skin care*. *Acta Derm Venereol*, 2013. **93** (3): p. 261-7.
58. Hachem, J.P., et al., *pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion*. *J Invest Dermatol*, 2003. **121** (2): p. 345-53.
59. Jang, H., et al., *Skin pH Is the Master Switch of Kallikrein 5-Mediated Skin Barrier Destruction in a Murine Atopic Dermatitis Model*. *Journal of Investigative Dermatology*, 2016. **136** (1): p. 127-135.
60. Ramesh, K., et al., *Exonic mutations associated with atopic dermatitis disrupt lympho-epithelial Kazal-type related inhibitor action and enhance its degradation*. *Allergy*, 2020. **75** (2): p. 403-411.
61. Baurecht, H., et al., *Epidermal lipid composition, barrier integrity, and eczematous inflammation are associated with skin microbiome configuration*. *J Allergy Clin Immunol*, 2018. **141** (5): p. 1668-1676.e16.

62. Boer, D.E.C., et al., *Σκιν οφ ατοπις δερματιτις πατιεντις σηωωσ διστυρβεδ β-γλυσοσερεβροσιδασε ανδ ασιδ σπηνωγομψελινασε αστιπψ τηατ ρελατες το σηανγες ιν στρατυμ ζορνειμ λιπιδ ζομποσιτιον*. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*, 2020. **1865** (6): p. 158673.
63. Seiti Yamada Yoshikawa, F., et al., *Exploring the Role of Staphylococcus Aureus Toxins in Atopic Dermatitis*. *Toxins*, 2019. **11** (6): p. 321.
64. Hülpiusch, C., et al., *Skin pH-dependent Staphylococcus aureus abundance as predictor for increasing atopic dermatitis severity*. *Allergy*, 2020. **75** (11): p. 2888-2898.
65. Elias, P.M., *The skin barrier as an innate immune element*. *Seminars in Immunopathology*, 2007. **29** (1): p. 3-14.
66. Ottman, N., et al., *Microbial and transcriptional differences elucidate atopic dermatitis heterogeneity across skin sites*. *Allergy*, 2020.
67. Gonzalez, T., et al., *Biofilm propensity of Staphylococcus aureus skin isolates is associated with increased atopic dermatitis severity and barrier dysfunction in the MPAACH pediatric cohort*. *Allergy*, 2020. **n/a** (n/a).
68. Di Domenico, E.G., et al., *Inflammatory cytokines and biofilm production sustain Staphylococcus aureus outgrowth and persistence: a pivotal interplay in the pathogenesis of Atopic Dermatitis*. *Scientific reports*, 2018. **8** (1): p. 9573-9573.
69. Krysko, O., et al., *Protease/antiprotease network in allergy: The role of Staphylococcus aureus protease-like proteins*. *Allergy*, 2019. **74** (11): p. 2077-2086.
70. Lacoma, A., et al., *Cigarette smoke exposure redirects Staphylococcus aureus to a virulence profile associated with persistent infection*. *Sci Rep*, 2019. **9** (1): p. 10798.
71. Oetjen, L.K. and B.S. Kim, *Interactions of the immune and sensory nervous systems in atopy*. *Febs j*, 2018. **285** (17): p. 3138-3151.
72. Guseva, D., et al., *Neuronal branching of sensory neurons is associated with BDNF-positive eosinophils in atopic dermatitis*. *Clin Exp Allergy*, 2020. **50** (5): p. 577-584.
73. Roesner, L.M., T. Werfel, and A. Heratizadeh, *The adaptive immune system in atopic dermatitis and implications on therapy*. *Expert Rev Clin Immunol*, 2016. **12** (7): p. 787-96.
74. Brunner, P.M., E. Guttman-Yassky, and D.Y. Leung, *The immunology of atopic dermatitis and its reversibility with broad-spectrum and targeted therapies*. *J Allergy Clin Immunol*, 2017. **139** (4s): p. S65-s76.
75. Eyerich, S., et al., *New biological treatments for asthma and skin allergies*. *Allergy*, 2020. **75** (3): p. 546-560.
76. Bieber, T., *Interleukin-13: Targeting an underestimated cytokine in atopic dermatitis*. *Allergy*, 2020. **75** (1): p. 54-62.
77. Brulefert, A., et al., *Vitamin D3-elicited CD14+ human skin dendritic cells promote thymic stromal lymphopoietin-independent type 2 T-helper responses*. *Allergy*, 2020.
78. Yamanishi, Y., et al., *Skin-infiltrating basophils promote atopic dermatitis-like inflammation via IL-4 production in mice*. *Allergy*, 2020. **75** (10): p. 2613-2622.
79. Murata, Y., et al., *Phase 2a, randomized, double-blind, placebo-controlled, multicenter, parallel-group study of a H4 R-antagonist (JNJ-39758979) in Japanese adults with moderate atopic dermatitis*. *J Dermatol*, 2015. **42** (2): p. 129-39.
80. Werfel, T., et al., *Efficacy and safety of the histamine H(4) receptor antagonist ZPL-3893787 in patients with atopic dermatitis*. *J Allergy Clin Immunol*, 2019. **143** (5): p. 1830-1837.e4.

81. Schaper-Gerhardt, K., et al., *The H(4) R is highly expressed on eosinophils from AD patients and IL-4 upregulates expression and function via the JAK/STAT pathway.* Allergy, 2020.
82. Karra, L., et al., *CD300a expression is modulated in atopic dermatitis and could influence the inflammatory response.* Allergy, 2019. **74** (7): p. 1377-1380.
83. Coates, M., et al., *The Skin and Intestinal Microbiota and Their Specific Innate Immune Systems.* Frontiers in Immunology, 2019.**10** (2950).
84. Ong, P.Y., et al., *Endogenous Antimicrobial Peptides and Skin Infections in Atopic Dermatitis.* New England Journal of Medicine, 2002.**347** (15): p. 1151-1160.
85. de Jongh, G.J., et al., *High expression levels of keratinocyte antimicrobial proteins in psoriasis compared with atopic dermatitis.* J Invest Dermatol, 2005. **125** (6): p. 1163-73.
86. Rieg, S., et al., *Deficiency of dermcidin-derived antimicrobial peptides in sweat of patients with atopic dermatitis correlates with an impaired innate defense of human skin in vivo.* J Immunol, 2005. **174** (12): p. 8003-10.
87. Nguyen, H.L.T., et al., *Role of Antimicrobial Peptides in Skin Barrier Repair in Individuals with Atopic Dermatitis.* Int J Mol Sci, 2020. **21** (20).
88. Maintz, L. and N. Novak, *Modifications of the innate immune system in atopic dermatitis.* J Innate Immun, 2011. **3** (2): p. 131-41.
89. Novak, N., et al., *Putative association of a TLR9 promoter polymorphism with atopic eczema.* Allergy, 2007. **62** (7): p. 766-72.
90. Skabytska, Y., et al., *How the innate immune system trains immunity: lessons from studying atopic dermatitis and cutaneous bacteria.* JDDG: Journal der Deutschen Dermatologischen Gesellschaft, 2016. **14** (2): p. 153-156.
91. Moriwaki, M., et al., *Σταπηφλοσορςςς αυρες φρομ ατοπς δερματιτς σκιν αςςυμυλατες ιν τηρ λψσοομοες οφ κερατινοςψτες ωιτη ινδυστιον οφ ΙΑ-1α σεςρετιον ια ΤΑΡ9.* Allergy, 2019. **74** (3): p. 560-571.
92. Janmohamed, S.R., et al., *Medical algorithm: Diagnosis of atopic dermatitis in early childhood (part I).* Allergy, 2021.**76** (1): p. 403-406.
93. Jacob, M., et al., *Quantitative profiling of cytokines and chemokines in DOCK8-deficient and atopic dermatitis patients.* Allergy, 2019. **74** (2): p. 370-379.
94. Rinaldi, A.O., et al., *Direct assessment of skin epithelial barrier by electrical impedance spectroscopy.* Allergy, 2019.**74** (10): p. 1934-1944.
95. Chopra, R., et al., *Efficacy of bleach baths in reducing severity of atopic dermatitis: A systematic review and meta-analysis.* Ann Allergy Asthma Immunol, 2017. **119** (5): p. 435-440.
96. Darrigade, A.S., et al., *Atopic Dermatitis Score 7 (ADS7): A promising tool for daily clinical assessment of atopic dermatitis.* Allergy, 2020. **75** (5): p. 1264-1266.
97. Nouwen, A.E.M., et al., *Natural moisturizing factor as a clinical marker in atopic dermatitis.* Allergy, 2020. **75** (1): p. 188-190.
98. Sun, Z., et al., *A Microbiome-Based Index for Assessing Skin Health and Treatment Effects for Atopic Dermatitis in Children.* mSystems, 2019. **4** (4): p. e00293-19.
99. Paller, A.S., et al., *The microbiome in patients with atopic dermatitis.* The Journal of allergy and clinical immunology, 2019.**143** (1): p. 26-35.
100. Kong, H.H., et al., *Performing Skin Microbiome Research: A Method to the Madness.* J Invest Dermatol, 2017. **137** (3): p. 561-568.

101. Thijs, J.L., et al., *Biomarkers detected in dried blood spots from atopic dermatitis patients strongly correlate with disease severity*. Allergy, 2019. **74** (11): p. 2240-2243.
102. Thijs, J.L., et al., *EASI p-EASI: Predicting disease severity in atopic dermatitis patients treated with cyclosporin A*. Allergy, 2019. **74** (3): p. 613-617.
103. Bakker, D.S., et al., *EASI p-EASI: Predicting disease severity in atopic dermatitis patients treated with dupilumab using a combination of serum biomarkers*. Allergy, 2020. **75** (12): p. 3287-3289.
104. Chen, S., et al., *AllergyGenDB: A literature and functional annotation-based omics database for allergic diseases*. Allergy, 2020.**75** (7): p. 1789-1793.
105. Baumann, R., et al., *Non-invasive and minimally-invasive techniques for the diagnosis and management of allergic diseases*.Allergy, 2020.
106. Pavel, A.B., et al., *Tape strips from early-onset pediatric atopic dermatitis highlight disease abnormalities in nonlesional skin*.Allergy, 2021. **76** (1): p. 314-325.
107. Breiteneder, H., et al., *Biomarkers for diagnosis and prediction of therapy responses in allergic diseases and asthma*.Allergy, 2020. **75** (12): p. 3039-68.
108. Czarnowicki, T., et al., *Evolution of pathologic T-cell subsets in patients with atopic dermatitis from infancy to adulthood*.Journal of Allergy and Clinical Immunology, 2020. **145** (1): p. 215-228.
109. Werfel T, H.A., Aberer W, Ahrens F, Augustin M, Biedermann T, Diepgen T, Fölster-Holst R, Kahle J, Kapp A, Nemat K, Peters E, Schlaeger M, Schmid-Grendelmeier P, Schmitt J, Schwennesen T, Staab D, Traidl-Hoffmann C, Werner R, Wollenberg A, Worm M, Ott H, *Update "Systemic treatment of atopic dermatitis" of the S2k-guideline on atopic dermatitis*. . J Dtsch Dermatol Ges, 2021. **Jan** (19): p. 151-168.
110. Looman, K.I.M., et al., *Associations of Th2, Th17, Treg cells, and IgA(+) memory B cells with atopic disease in children: The Generation R Study*. Allergy, 2020. **75** (1): p. 178-187.
111. Avena-Woods, C., *Overview of atopic dermatitis*. Am J Manag Care, 2017. **23** (8 Suppl): p. S115-s123.
112. Wollenberg, A., et al., *Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I*. J Eur Acad Dermatol Venereol, 2018. **32** (5): p. 657-682.
113. Wollenberg, 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): p. 850-878.
114. Nakahara, T., et al., *Treatment satisfaction in atopic dermatitis relates to patient-reported severity: A cross-sectional study*. Allergy, 2019. **74** (6): p. 1179-1181.
115. Sindher, S., et al., *Pilot study measuring transepidermal water loss (TEWL) in children suggests trilipid cream is more effective than a paraffin-based emollient*. Allergy, 2020. **75** (10): p. 2662-2664.
116. Nilsson, E.J., C.G. Henning, and J. Magnusson, *Topical corticosteroids and Staphylococcus aureus in atopic dermatitis*. J Am Acad Dermatol, 1992. **27** (1): p. 29-34.
117. Gonzalez, M.E., et al., *Cutaneous microbiome effects of fluticasone propionate cream and adjunctive bleach baths in childhood atopic dermatitis*. J Am Acad Dermatol, 2016. **75** (3): p. 481-493.e8.
118. Blanchet-Réthoré, S., et al., *Effect of a lotion containing the heat-treated probiotic strain Lactobacillus johnsonii NCC 533 on Staphylococcus aureus colonization in atopic dermatitis*. Clinical, cosmetic and investigational dermatology, 2017. **10** : p. 249-257.
119. Myles, I.A., et al., *First-in-human topical microbiome transplantation with Roseomonas mucosa for atopic dermatitis*. JCI Insight, 2018. **3** (9).
120. Parlet, C.P., M.M. Brown, and A.R. Horswill, *Commensal Staphylococci Influence Staphylococcus aureus Skin Colonization and Disease*. Trends Microbiol, 2019. **27** (6): p. 497-507.

121. Williams, M.R., et al., *Quorum sensing between bacterial species on the skin protects against epidermal injury in atopic dermatitis*. Science Translational Medicine, 2019. **11** (490): p. eaat8329.
122. Paharik, A.E., et al., *Coagulase-Negative Staphylococcal Strain Prevents Staphylococcus aureus Colonization and Skin Infection by Blocking Quorum Sensing*. Cell host & microbe, 2017. **22** (6): p. 746-756.e5.
123. Luu, L.A., et al., *Apple cider vinegar soaks [0.5%] as a treatment for atopic dermatitis do not improve skin barrier integrity*. Pediatric Dermatology, 2019. **36** (5): p. 634-639.
124. Sawada, Y., et al., *Dilute bleach baths used for treatment of atopic dermatitis are not antimicrobial in vitro*. J Allergy Clin Immunol, 2019. **143** (5): p. 1946-1948.
125. Silva, S.H., et al., *Influence of narrow-band UVB phototherapy on cutaneous microbiota of children with atopic dermatitis*. J Eur Acad Dermatol Venereol, 2006. **20** (9): p. 1114-20.
126. Clowry, J., A.D. Irvine, and R.M. McLoughlin, *Next-generation anti-Staphylococcus aureus vaccines: A potential new therapeutic option for atopic dermatitis?* Journal of Allergy and Clinical Immunology, 2019. **143** (1): p. 78-81.
127. Siegels, D., et al., *Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis*. Allergy, 2020.
128. Siegels, D., et al., *Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis*. Allergy, 2020.
129. Le Floch, A., et al., *Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4/IL-13 antibody, is required to broadly inhibit type 2 inflammation*. Allergy, 2020. **75** (5): p. 1188-1204.
130. Rohner, M.H., et al., *Dupilumab reduces inflammation and restores the skin barrier in patients with atopic dermatitis*. Allergy, 2020.
131. Ariens, L.F.M., et al., *Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry*. Allergy, 2020. **75** (1): p. 116-126.
132. Pfaller, B., et al., *Biologics in atopic disease in pregnancy: An EAACI position paper*. Allergy, 2021. **76** (1): p. 71-89.
133. Spektor, L.S., et al., *Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: Results from the BioDay registry*. Allergy, 2020. **75** (9): p. 2376-2379.
134. Agache, I., et al., *Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: A systematic review for the EAACI biologics guidelines*. Allergy, 2021. **76** (1): p. 45-58.
135. Chen, X., et al., *Treatment-emergent adverse events in dupilumab-treated patients with allergic diseases: A meta-analysis*. Allergy, 2021. **76** (2): p. 593-596.
136. Jonstam, K., et al., *Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyps*. Allergy, 2019. **74** (4): p. 743-752.
137. Nettis, E., et al., *Efficacy of dupilumab in atopic comorbidities associated with moderate-to-severe adult atopic dermatitis*. Allergy, 2020. **75** (10): p. 2653-2661.
138. Akdis, C.A., et al., *Type 2 immunity in the skin and lungs*. Allergy, 2020. **75** (7): p. 1582-1605.
139. Kang, E.G., et al., *Efficacy and safety of mepolizumab administered subcutaneously for moderate to severe atopic dermatitis*. Allergy, 2020. **75** (4): p. 950-953.
140. Wegner, J., et al., *IgE-specific immunoadsorption: New treatment option for severe refractory atopic dermatitis*. Allergy, 2019. **74** (6): p. 1190-1193.

141. Weidner, J., et al., *Spotlight on microRNAs in allergy and asthma*. Allergy, 2020.
142. Vaher, H., et al., *miR-10a-5p is increased in atopic dermatitis and has capacity to inhibit keratinocyte proliferation*. Allergy, 2019. **74** (11): p. 2146-2156.
143. Hayashi, K., et al., *LAT1-specific inhibitor is effective against T cell-mediated allergic skin inflammation*. Allergy, 2020. **75** (2): p. 463-467.
144. Bieber, T., et al., *Unraveling the complexity of atopic dermatitis: The CK-CARE approach toward precision medicine*. Allergy, 2020. **75** (11): p. 2936-2938.
145. Perrett, K.P. and R.L. Peters, *Emollients for prevention of atopic dermatitis in infancy*. The Lancet, 2020. **395** (10228): p. 923-924.
146. Skjerven, H.O., et al., *Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial*. The Lancet, 2020. **395** (10228): p. 951-961.
147. Chalmers, J.R., et al., *Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial*. The Lancet, 2020. **395** (10228): p. 962-972.
148. Horimukai, K., et al., *Application of moisturizer to neonates prevents development of atopic dermatitis*. J Allergy Clin Immunol, 2014. **134** (4): p. 824-830.e6.
149. Simpson, E.L., et al., *Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention*. J Allergy Clin Immunol, 2014. **134** (4): p. 818-23.
150. Kothari, A., A. Locke, and T. Eiwegger, *Emollients for the prevention of atopic dermatitis*. Allergy, 2020.
151. Lack, G., et al., *Factors associated with the development of peanut allergy in childhood*. N Engl J Med, 2003. **348** (11): p. 977-85.
152. Nicklaus, S., et al., *The protective effect of cheese consumption at 18 months on allergic diseases in the first 6 years*. Allergy, 2019. **74** (4): p. 788-798.
153. Venter, C., et al., *EAACI position paper on diet diversity in pregnancy, infancy and childhood: Novel concepts and implications for studies in allergy and asthma*. Allergy, 2020. **75** (3): p. 497-523.
154. Rusu, E., et al., *Prebiotics and probiotics in atopic dermatitis*. Experimental and therapeutic medicine, 2019. **18** (2): p. 926-931.
155. Gibson, G.R. and M.B. Roberfroid, *Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics*. J Nutr, 1995. **125** (6): p. 1401-12.
156. Hill, C., et al., *Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic*. Nat Rev Gastroenterol Hepatol, 2014. **11** (8): p. 506-14.
157. Amalia, N., et al., *Systematic review and meta-analysis on the use of probiotic supplementation in pregnant mother, breastfeeding mother and infant for the prevention of atopic dermatitis in children*. Australas J Dermatol, 2020. **61** (2): p. e158-e173.
158. Roßberg, S., et al., *Orally applied bacterial lysate in infants at risk for atopy does not prevent atopic dermatitis, allergic rhinitis, asthma or allergic sensitization at school age: Follow-up of a randomized trial*. Allergy, 2020. **75** (8): p. 2020-2025.
159. Garcia-Larsen, V., et al., *Diet during pregnancy and infancy and risk of allergic or autoimmune disease: A systematic review and meta-analysis*. PLoS Med, 2018. **15** (2): p. e1002507.

160. Li, L., et al., *Probiotic Supplementation for Prevention of Atopic Dermatitis in Infants and Children: A Systematic Review and Meta-analysis*. *Am J Clin Dermatol*, 2019. **20** (3): p. 367-377.

Figure captions

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

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 the future.