Atopic Eczema: Pathophysiological Findings as the Beginning of a New Era of Therapeutic Options

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Contents

Abstract

Atopic eczema (AE) is a chronic inflammatory disease hallmarked by intense pruritus and eczematous lesions. It depicts one of the most common skin diseases affecting a major part of children and several percentages of adults.

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Both pathogenesis and pathophysiology are based on complex orchestrated interactions of skin barrier defects, immunological changes, the environment, and an abundance of other contributing factors. Frequently, AE displays the starting point for other allergic diseases such as allergic asthma and rhinoconjunctivitis. Additionally, the risk of developing food allergy is increased. Furthermore, the disease is accompanied by a susceptibility to bacterial, fungal, and viral infections. The development of new therapies received great impetus by an ample research of the pathophysiological mechanisms, leading to a new era in the treatment of severe atopic eczema due to targeted treatments, e.g. the IL-4R alpha specific monoclonal antibody dupilumab.

This article provides an overview of the causative and pathophysiological characteristics, the clinical and diagnostic aspects as well as current and future therapeutical possibilities focusing allergic aspects contributing to the course of the disease.

1 Introduction

Atopic eczema (AE), also known as atopic dermatitis, depicts one of the most common chronic inflammatory skin diseases affecting nearly one in five individuals in industrialized countries (Weidinger and Novak 2016; Flohr and Mann 2014; Werfel et al. 2016). The disease was first described by Robert Willan in 1808 and characterized in detail by Ernest Henri Besnier in 1892 (Besnier 1892). The term "atopic" classifies AE as a disease belonging with allergic asthma, allergic rhinoconjunctivitis, and food allergy to the spectrum of atopic diseases, first described in 1922 by the allergists Arthur F. Coca and Robert A. Cooke (1923).

Regarding the disease prevalence, an increase has become apparent in the last decades, especially in industrialized countries. As in most countries, over 20% of the children are affected at least during a period of their lives. In adulthood the prevalence ranges from 1 to 10% considering distinct regional variations and based on the definition of AE in the data collection (Flohr and Mann 2014; Dizon et al. 2018). Around 60% of all cases manifest within the first year and additionally 85% before the age of five; however, AE can emerge lifelong (Garmhausen et al. 2013; Vakharia and Silverberg 2019; Abuabara et al. 2019). Large birth cohort studies revealed that most of the children affected by AE have a mild disease severity; however, moderate to severe AE can persist into adulthood in individual cases, particularly in children early and severely affected and that are sensitized to various allergens in infancy and early childhood. Register studies are needed to investigate the persistence of AE beyond the youth (Bieber et al. 2020).

Combined with other allergic diseases, AE impacts the socioeconomics heavily (Chung and Simpson 2019). However, the intense burden is reported not only for the economy but also for the life quality, especially in patients with severe AE, as, e.g.,

levels of anxiety and depression are higher in those patients (de Bruin-Weller et al. 2020).

2 Pathogenesis and Pathophysiology

The pathogenesis of AE is orchestrated by a complex interaction between genetic predisposition and the environmental aspects (Gilles et al. 2018).

2.1 Genetics

The genetic burden depicts a major factor for developing AE, which is emphasized by a concordance of 80% in monozygous twins and 20% in heterogenous ones. Genetic analyses of AE patients have revealed a multitude of different mutations, especially in genes of barrier proteins and immunological pathways. In 2015, Paternoster et al. identified additional 10 risk loci maximizing the number to 31, e.g. in the filaggrin gene, in cytokine molecules and receptors like IL-13 and IL6R, and in signaling proteins as STAT3 (Paternoster et al. 2015). However, less than 20% of the estimated heritability can be explained by the identified susceptibility loci (Weidinger and Novak 2016). The most prominent risk factors are loss-of-function mutations in the filaggrin gene. This gene encodes a protein which is essential not only for a functional skin barrier but also for the homoeostasis of the epidermis. A filaggrin loss-of-function mutation increases the risk for AE by a factor of 3.12–4.78 (Irvine et al. 2011; van den Oord and Sheikh 2009). Noteworthy, roughly 60% of mutation carriers in the whole population do not develop AE (Weidinger and Novak 2016; Irvine et al. 2011).

2.2 Environment

The impact of environmental and social factors is underlined by investigations showing an increased risk due to treatment with antibiotics in pregnancy and early childhood (Penders et al. 2014), smaller families and classes of higher socioeconomic status (Ofenloch et al. 2019), and a reduced diversity of the microbiota in the gut (Wang et al. 2008). Additionally, indoor (Kim et al. 2015; Kwon et al. 2015; Lee et al. 2011) and outdoor air pollution (Huang et al. 2015) as well as psychosocial stress may contribute to an increased risk for AE (Gilles et al. 2018). Concerning the development of allergies, the skin exposure with peanut proteins in household dust may elevate the risk of developing a peanut allergy in children with AE or those carrying a filaggrin loss-of-function mutation (Brough et al. 2015).

2.3 Pathophysiology

Pathophysiologically, these aspects, combined with a complex interaction of skin barrier defects and an inadequate immune response, are assumed to lead to the clinical picture of AE (Weidinger and Novak 2016). The immunological hallmark of AE lesions is a Th2 polarized inflammation infiltrate. Type 2 skewing of Th cells and other immune cells (cytotoxic T lymphocytes, innate lymphoid cells) are induced by different factors. Keratinocytes produce augmented amounts of thymic stromal lymphopoietin (TSLP) in AE skin priming naïve T cells toward Th2 via dendritic cells (Oyoshi et al. 2010). Furthermore, pollen, which can penetrate the disrupted skin barrier easily, contribute to a type 2 cytokine milieu, among others by inhibiting IL-12 production (Aglas et al. 2018; Traidl-Hoffmann et al. 2005).

Concerning the skin, different abnormalities are reported in AE: an increased transepidermal water lass (TEWL) (Flohr et al. 2010), changes in lipid composition and stucture (Ishikawa et al. 2010; Janssens et al. 2012), and elevated activity of skin serine proteases (Weidinger and Novak 2016; Voegeli et al. 2009). Further, changes of the skin microbiome are present, especially a reduced skin microbiome diversity and augmented amounts of Staphylococcus aureus (S. aureus) colonizing the surface (Reiger et al. 2019). Recently, it was shown that the abundance of, Staphylococcus aureus (S. aureus) correlates with the expression of skin barrier proteins, revealing the importance of the skin microbiome in the pathophysiology of AE (Altunbulakli et al. 2018). However, not just the skin microbiome, but also the gut bacteria seem to contribute to the pathophysiology of AE. Bifidobacterium counts are lower in AE patients and, additionally, Faecalibacterium prausnitzii subspecies are highly related to AE (Watanabe et al. 2003; Song et al. 2016; Reiger et al. 2020). Several studies revealed that the aberrations of the gut microbiome precede the onset of AE. It is part of ongoing research to which extension the altered gut microbiome contributes to the development of the disease and a Th2 skewing of cutaneous inflammation.

The immunological hallmarks of AE led to a dichotomic subgrouping into an intrinsic ("non-allergic") and extrinsic ("allergic") form of the disease. The latter was defined by an increased total IgE in serum, detectable allergen-specific IgE antibodies against aero- and food allergens, and association with IgE mediated clinical reactions and other atopic diseases (Novak and Bieber 2003; Johansson et al. 2001). Contrarily, 16–45% of adult patients with AE reveal neither specific sensitizations nor elevated total IgE and thus suffer from the intrinsic form (Schmid-Grendelmeier et al. 2001). Notably, in infants (age 0–2 years) the prevalence of the intrinsic form approaches 60% (Park et al. 2006), suggesting that normal total IgE and lack of allergen-specific IgE antibodies, respectively, may only be present in the inception of the disease. Therefore, this dichotomic approach has become blurred and the concept of the differentiation of endotypes of the disease has risen (Eyerich et al. 2019; Czarnowicki et al. 2019).

Besides IgE against environmental allergens, a multitude of IgE reactive to self-proteins was described under the term "autoallergy" (Hradetzky et al. 2014; Roesner and Werfel 2019). Autoallergic phenomena appear specific in AE and may contribute to the inflammation (Hradetzky et al. 2015). T cells reactive to autoallergens

produce, besides the common type 2 cytokines IL-4 and IL-13, type 1 inflammation proteins such as IFN-γ and other cytokines such as IL-17 and IL-22 (Hradetzky et al. 2014; Roesner et al. 2016).

Interestingly, not just a type 2 polarized inflammation can be detected in AE lesions, but Th1 cytokines are upregulated in subacute and chronic lesions of adult patients as well (Werfel et al. 1996). In the lesional skin of children, Brunner et al. showed additionally to the Th2 profile an increase of Th17 and Th22 cytokines (Brunner et al. 2018). Additionally, alterations can be detected concerning different ethnical backgrounds, as the Asian AE can be hallmarked, besides a Th2 profile, by a pronounced Th17 inflammation providing some characteristics known from psoriasis (Noda et al. 2015).

In conclusion, a myriad of different aspects concerning genetics, immunology, environment, and skin barrier and their interaction have been identified to contribute to the complex picture of AE's pathogenesis and pathophysiology so far.

3 Clinical Symptoms

The clinical manifestations of AE are diverse. In addition to scratch induced excoriations and crustae caused by pruritus, the disease is characterized by inflammatory lesions with epidermal involvement "eczematous" skin lesions. In most patients these lesions do not occur before the age of two months (Weidinger and Novak 2016). The distribution pattern of lesions on the integument varies with age, leading to the differentiation of three phases: In infancy eczematous lesions are predominant in the face and capillitium and, furthermore, frequently combined with exudative crusted erosions, which are associated with superinfections caused most prominently by S. aureus (Alexander et al. 2020). The diseases hallmarks in childhood are focused at the cubital and popliteal folds being less exudative than in infants (Traidl and Werfel 2019). In the adulthood, the accented areas are symmetrical around the head, neck, and flexure folds (Fig. 1a, b) (Coors 2016). Furthermore, acute lesions are accompanied by oozing, as chronic AE lesions provide the picture of lichenification, meaning coarsening of the skin markings (Finlay et al. 1980).

The disease is characterized by recurrent flares induced by a multitude of factors, e.g. stress or bacterial skin infections. Double-blinded, placebo-controlled studies revealed an exacerbation of the disease due to aeroallergens and food allergens in sensitized patients (Werfel et al. 2015; Wassmann-Otto et al. 2018).

4 Diagnosis

Due to the fact that laboratory markers are not available, the diagnosis of AE can only be based on clinical features. The diagnostic criteria of Jon M. Hanifin and Georg Rajka published in 1980 are still the basis for the diagnosis and most frequently used in clinical trials (Vakharia et al. 2018; Hanifin and Rajka 1980).

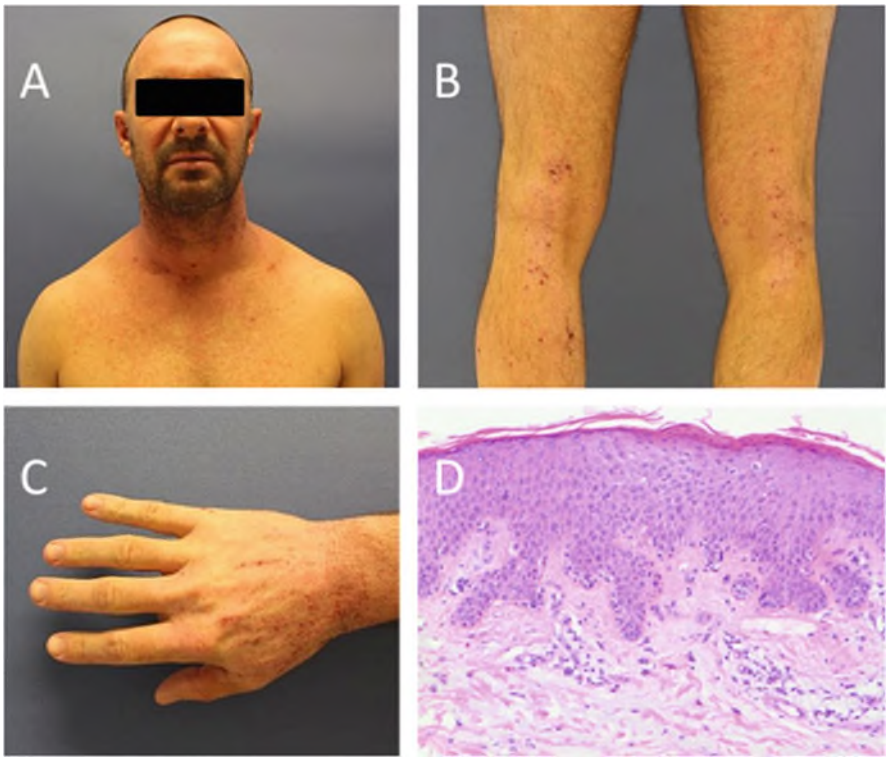

Fig. 1 Skin manifestations of AE and histological abnormalities. (**a**) Typical head and neck involvement in an adult male AE patient. (**b**) Flexural papules with scratch excoriations and lichenification. (**c**) AE affecting the hand characterized by intense pruritic, eczematous lesions. (**d**) Histological changes of AE: The biopsy reveals parakeratosis, moderate acanthosis, spongiosis, and an assorted infiltrate with several eosinophils and melanophages (Image **d** is kindly provided by PD Dr. med. V. Schacht)

The major criteria involve pruritus, eczematous lesions (Fig. 1c) on the disease and age typical spots, a chronic or relapsing course of disease, and a personal or family history of atopic diseases. Additionally, 23 minor criteria exist, such as elevated total IgE or the Dennie-Morgan infraorbital fold (Braun-Falco et al. 2005). Both exemplary minor criteria represent the allergic aspect of the disease, as they can be found in patients with allergic rhinoconjunctivitis as well. The diagnosis of AE can be made based on at least three major criteria accompanied by three minor criteria (Hanifin and Rajka 1980). In 1994 the U.K. Working Party published their refinement of the Hanifin and Rajka criteria containing a minimum of criteria for the AE diagnosis (Williams et al. 1994). Therefore, a detailed history combined with the skin inspection and an IgE measurement is the key point for the diagnosis. Additionally, the latter is important, as sensitizing against aero- and food allergens can lead to flares of the AE (Werfel et al. 2015; Wassmann-Otto et al. 2018). Whilst food allergies in young AE children, e.g. to hen's egg, milk, and

wheat, depict the most common ones, in adults cross allergy to, e.g., nuts due to sensitization against aeroallergens are more prevalent (Wassmann and Werfel 2015). Consequently, there is a shift from food allergens to aeroallergens from young to adult AE patients, which is, however, not obligate, since some adult patients with AE can still suffer from food allergies and some young children can already develop inhalant allergies. Several double-blinded, placebo-controlled studies emphasized the deteriorative effect of allergens to sensitized patients measured by clinical skin scores as SCORAD and EASI (Werfel et al. 2015; Breuer et al. 2004; Werfel and Kapp 1998).

Histological analysis of skin biopsies showing spongiosis, mild acanthosis, orthokeratosis, and a lymphohistiocytic infiltrate with eosinophils and several melanophages can complete the diagnosis. Dermatohistopathology is, however, of minor importance for the diagnosis of AE compared to other clinical features in clear presentations of symptoms (Fig. 1d).

Different scores are suitable for measuring the clinical severity of AE: Eczema Area and Severity Index (EASI), Patient-oriented Eczema Measure (POEM), and Severity Scoring of Atopic Dermatitis (SCORAD) index (Schmitt et al. 2007). Regarding the SCORAD, besides the distribution of the affected body surface, erythema, edema/papulation, oozing/crusts, excoriations, lichenification, and xerosis are assessed for objective scores, while the extent of pruritus and sleeplessness are measured as subjective parameters. The EASI score focuses on the objective parameters such as erythema, edema and papulation, lichenification, and excoriation allocated with the four areas head, upper extremities, body, and lower extremities (Kunz et al. 1997). To focus on subjective parameters of the disease, the Patient-Oriented Eczema Measures for Eczema (POEM) is frequently used. All three scores, SCORAD, POEM, and EASI, are currently applied in clinical trials.

5 Comorbidities and Complications: From Allergy to Infections

As mentioned before, AE depicts one of the four diseases of the atopic circle. Gustafsson et al. investigated the development of other atopic diseases of AE affected children. 94 children were examined for seven years, revealing that nearly 90% of the patients experienced an improvement of the skin manifestations; however, 43% developed allergic asthma and 45% allergic rhinoconjuncitivits (Gustafsson et al. 2000). Interestingly, an early onset of AE is associated with an increased risk of a sensitization against aeroallergens. Additionally, 5,729 patients born in 1961 were followed up until 2004 by Martin et al. (Martin et al. 2011). It was shown that manifesting an AE before the age of seven increases the risk to develop an allergic asthma in adulthood and that the disease persists beyond childhood when developing an asthma as a child. It is hypothesized that the barrier defects, which are caused, among others, by the insufficient expression of filaggrin, allow a sensitization against aeroallergens. The German multicenter allergy study (MAS), observing 1,314 newborns until the age of twenty, showed an increased risk of developing

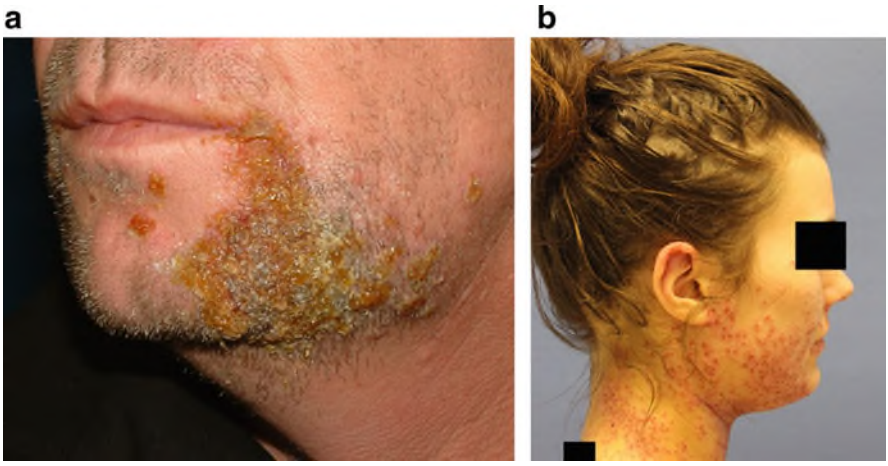

Fig. 2 Infectious complications of AE patients. (**a**) Staphylococcal superinfection of AE lesion. (**b**) Eczema herpeticum: grouped scattered erythematous erosions and vesicles presented in a young female AE patient

allergies and allergic disease if at least two closer family members suffer from AE, another atopic manifestation or an increased IgE in the cord blood (Lau et al. 2002). Interestingly, eczema was still present in 10% of all young women and 4 % in young men at the age of 20 in members of this atopic birth cohort (Gough et al. 2015).

In conclusion, AE often depicts the first step of an allergic burden, followed by allergic rhinoconjunctivitis and allergic asthma as well as food allergy. This development is called "atopic march."

Additionally, AE patients are prone to viral and bacterial infections. Bacterial infections with especially group A Streptococcus inducing impetigo contagiosa (see Fig. 2a) and S. aureus superinfections are common in those subjects.

Concerning viral susceptibility, disseminated clinical manifestations of herpes simplex virus (HSV), molluscum contagiosum virus (MCV), human papillomavirus (HPV), and vaccinia virus can appear. Most prominently, the spread of herpes vesiculae known as eczema herpeticum (EH) (see Fig. 2b) can be accompanied by systemic symptoms such as fever and malaise and may lead to life-threatening complications when HSV affects the brain (herpes encephalitis) and liver (herpes hepatitis) (Traidl et al. 2018, 2021; Seegräber et al. 2020).

These viral disseminations affect around 7–10% of AE patients (Beck et al. 2009). Noteworthy, AE is defined as a contraindication for the vaccination with vaccinia virus due to the viral susceptibility (Grabenstein and Winkenwerder 2003). Additionally, not only skin affecting viral diseases but also extra dermal diseases are more prevalent in AE, as high-risk HPV is more common in AE in cervical cytology (Morgan et al. 2015).

Beside somatic comorbidities, a high number of studies focused on psychiatric comorbidities in AE patients. Schmitt et al. analyzed large cohorts of patients, investigating the prevalence of attention-deficit/hyperactivity disorder (ADHD) in

600,000 German children and adolescents. They showed that the prevalence in AE patients was significantly increased with 5.2% compared to 3.4% in healthy individuals (Schmitt et al. 2009). An increased prevalence of ADHD in AE was confirmed by a couple of other independent studies from different countries. Further prospective data revealed that infants with AE suffer from an elevated risk for mental health problems at age 10. Importantly, despite clearing after the age of two years, AE may cause persistent emotional and behavioral complications (Schmitt et al. 2010). There is a significant correlation of earlier use of antihistamines and ADHD symptoms (OR 1.88; 95%-CI: 1.04–3.39) (Schmitt et al. 2018). However, not just ADHD, but also depression (1.81; 95% CI, 1.33–2.46), anxiety (1.77; 95% CI, 1.36–2.29), conduct disorder (1.87; 95% CI, 1.46–2.39), and autism (3.04; 95% CI, 2.13–4.34) were found to be significantly increased in AE (Yaghmaie et al. 2013). Additionally, AE is associated with an increased prevalence of suicidal ideation in children and adults (OR 4.32; 95% CI, 1.93–9.66).

6 Therapy

Based on the chronic relapsing character of the disease, the treatment of AE can be challenging.

The use of moisturizers displays the basis of all therapeutical concepts for AE. As most cases of AE are mild, moisturizers supported by topical steroids, calcineurin inhibitors and, only approved in the USA, topical phosphodiesterase 4 inhibitors are sufficient to control the disease. Additionally, a proactive use, meaning a long-term, low-dose intermittent application of topical steroids or calcineurin inhibitor twice per week even if no active lesions are visible, has proven to reduce exacerbations (Berth-Jones et al. 2003; Wollenberg and Ehmann 2012). Furthermore, AE patients should be educated regarding the benefit of topical and systemic treatments and the avoidance of trigger factors of the disease. Controlled studies revealed not just an increase of the quality of life by patient education intervention but also a significant disease improvement in children, adolescents, and adults taking part in structured patient education programs for AE such as Arbeitsgemeinschaft Neurodermitisschulung (AGNES) or Arbeitsgemeinschaft Neurodermitisschulung für Erwachsene (ARNE) (Heratizadeh et al. 2017; Staab et al. 2006). As AE is more prevalent in children, educational concepts training children and their caregivers are of importance (for a differentiated view on this topic, see: Handbook of Experimental Pharmacology on Allergy: Patient/Relative Education).

However, for chronic or frequently recurrent moderate to severe forms of AE topical treatment alone may be insufficient. For those patients, additional systemic therapy is needed. Until 2017, systemic steroids and ciclosporin were the only approved therapy options in AE (Schmitt et al. 2017). The off-label use of other immune suppressive treatments, e.g. methotrexate, mycophenolate mofetil, or azathioprine was rare. With the approval of dupilumab, a human monoclonal IgG4 antibody targeting the a-chain of the IL-4 and IL-13 receptor, the first biological is available for the treatment of AE. It has a comprehensive label by the EMA as it

"[. . .] is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are candidates for systemic therapy" (European Medicines Agency 2018). In the dupilumab phase III studies 1,379 patients with moderate to severe atopic dermatitis were treated with 300 mg subcutaneous every week, every other week or placebo (Simpson et al. 2016). The primary endpoint of total or nearly complete remission after 16 weeks was achieved by 36–38% of the patients in the intervention groups intervention groups. An EASI-75, meaning an improvement of the EASI score compared to baseline of at least 75%, was prevalent in 44–51% of patients after 16 weeks of treatment with dupilumab. Data from the German registry on adult patients with AE ("TREATgermany") recently confirmed comparable efficacy of dupilumab in the "real world." (Abraham et al. 2020) In comparison, the EASI-75 of ciclosporin after 12 weeks was shown to be around 34% in this registry before (Schmitt et al. 2017). The most common adverse event of dupilumab is conjunctivitis. Interestingly, this is a disease specific side effect, as it is not observed in the dupilumab studies in asthma or polyposis nasi patients (Castro et al. 2018; Bachert et al. 2016). It should be mentioned that the risk of eczema herpeticum is reduced under the treatment with dupilumab probably due to its positive effect on the overall skin condition (Fleming and Drucker 2018).

Of note, dupilumab depicts just the beginning of a new era of innovative treatment options for moderate to severe AE patients who cannot be treated sufficiently with topical applications and phototherapy. Besides monocloncal antibodies against major type 2 inflammation associated cytokines, e.g. IL-13, IL-22, and IL-31, other molecules are targeted such as OX-40 and TSLP by antibodies or small molecules (Honstein and Werfel 2020). Additionally, cytokine receptor associated kinases, namely Janus kinases, are inhibited by several promising drugs leading to the interruption of different cytokine pathways. Most recently, the histamine (H) 4 receptor was identified as a potential target and positive effect concerning the disease severity on blocking the receptor was revealed in a clinical proof of concept trial with nearly 100 patients with AE (Schaper-Gerhardt et al. 2018; Werfel et al. 2019).

7 Resume and Outlook

The research of AE has received great impetus over the last decades. The improved understanding of the pathophysiology, the involved cells, and cytokines in addition to the increasing prevalence led to a multiplicity of different new therapy options in the pipeline. In the last years it has become more and more clear that the disease, besides the quite uniform clinical manifestation, consists of different disease endotypes. It will be important to use the new and upcoming research techniques to identify different endotypes of the disease and provide a tailored therapy for the individual patient. Due to the rising prevalence of allergies and the connection of AE with atopic comorbidities an all-embracing therapeutical approach is needed.

However, even more important is a preventive view on the disease. Especially the intervention in early childhood in high-risk infants seems to be fundamental.

In conclusion, AE is a disease with a high socioeconomic and individual impact and can be accompanied by a multitude of comorbidities and complications. A sufficient treatment, especially with new therapeutically possibilities, is needed. Therefore, further research is important to have the ability to tailor the treatment to the patient's endotype.

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