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Abstract

The immune system has vital functions for homeostasis and host defense. Thus, imbalances of the immune system whether associated with allergy, hypersensitivity, or autoimmunity are of great importance, as is manifest from common diseases such as atopic diseases, urticaria, and angioedema, and drug hypersensitivity reactions. These can affect patients' quality of life and can generate high costs for health care. Epidemiological studies have provided evidence for changing patterns of allergic diseases caused by lifestyle and climate changes which have consequences for medical care. Deeper insights into the pathogenesis of allergic/immunologic diseases, combined with novel technologies, provide improved diagnostic options and treatment measures. This review will summarize novel aspects of the epidemiology, pathogenic mechanisms, as well as disease management in the fields of allergy and clinical immunology.

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Introduction

Allergic diseases that have long been associated with the Western lifestyle show an increasing prevalence in India and Asia. In these areas, huge efforts are being made to investigate the sensitization and disease patterns, which are a prerequisite to organize adequate health care, e.g., diagnostic and therapeutic options and standards. Further information on the effects of lifestyle changes and environment on allergen sensitization and the manifestation of allergic diseases has been derived by analyzing the changing allergy status of immigrants to Western countries. This epidemiologic data together with recent insights into the pathogenesis of immune reactions provide new strategies for the management of diseases such as allergic rhinitis (AR), asthma, atopic dermatitis (AD), mast cell-driven diseases, and drug allergy. This review will summarize the novel aspects of the epidemiology, pathogenic mechanisms, as well as diagnostics and treatment in the field of allergy and clinical immunology (Fig. 1).

The Effects of the Environment on Atopic Diseases

Studying the pattern of allergic diseases in immigrants can provide further insight into the role of environment. First-generation immigrants have a lower allergy preva-

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Fig. 1. Overview of the main research developments in the fields of allergy and clinical immunology demonstrating the originality and interrelation of epidemiological insights [1–32], basic and translational research results [33–95] with practical applications useful for improved diagnostics [96–118] and therapy [80, 119–153].

lence as compared to the native population, and the risk of atopy increases with duration of residence, younger age at migration, or birth after migration as compared to migration after birth [1]. A relatively low atopy risk was shown in migrants moving from less affluent to affluent countries or from rural to urban areas [1]. In addition to hereditary predisposition, lifestyle factors such as a farming environment, smoking, family size, body weight, or frequency of colds significantly influenced the immunoglobulin (Ig)E-sensitization rate and pattern in adolescents [2]. Moreover, a role of environmental exposure, in particular climate, in the sensitization pattern to perennial and seasonal allergens has been reported in France [3]. In order to elucidate the mechanisms by which early-life risk factors influence the allergy risk in children, DNA methylation was investigated. Mean methylation levels of the promoter region of interferon (IFN)- γ were significantly higher in children at 6 years with AR compared to those without AR [4]. Hence, methylation levels are believed to have a mediating role in the association between season of birth and AR [4].

High-sensitivity C-reactive protein (hs-CRP) is considered a marker for a low-grade inflammation that is linked to non-communicable diseases, of which childhood allergic diseases are the earliest ones to appear. The relationship between hs-CRP and allergic diseases was studied in two large population-based German birth cohorts. However, this study did not reveal any significant association between hs-CRP levels and any of the studied allergic outcomes such as asthma, eczema, AD, food sensitization, or aeroallergen sensitization [5].

The prevalence of allergic diseases is increasing in Eastern and Asian countries and has become a major health concern. In South Turkey, a statistically significant increase in the prevalence of physician-diagnosed allergic diseases between 1994 and 2014 has been reported [6]. On the Indian subcontinent, the spectrum of allergens is highly diverse due to the varied climate, flora, and food habits. Therefore, in order to facilitate an accurate diagnosis and to design vaccines for immunotherapy, proper identification, purification, and molecular characterization of allergy-eliciting molecules are essential [7]. In China, the geo-

graphical distribution pattern of both allergic asthma and rhinitis with *Dermatophagoides* sensitization is dependent on the annual mean temperature and humidity [8]. For distinct regions, e.g., central China, a minimal standard skin prick test (SPT) series with eight allergens has been developed that guarantees identification of 99% of sensitized patients [9]. Translation and validation of a Chinese version of the score for AR (SFAR) enables estimation of AR prevalence in epidemiological studies and comparability with international data [10]. In Singapore, three maternal dietary patterns have been observed, of which the seafood and noodles pattern was associated with a reduced risk of developing allergen sensitization at both 18 months and 36 months after adjustment for other allergy-associated factors [11]. On the other hand, the patterns of vegetables, fruit, and white rice or pasta, cheese, and processed meat did not show any association [11]. A meta-analysis found a sex difference for AR prevalence, with a male predominance in childhood and female predominance in adolescence worldwide except for Asia [12].

Atopic Diseases and Comorbidities

A bidirectional relationship between psychosocial factors and allergic or atopic diseases has been reported in several studies. This observation could be confirmed by a study investigating the associations of psychosocial factors such as social status, depression, generalized anxiety, psychosocial stress, and type-D personality, with development of seasonal, perennial, and other allergies in adults [13]. Interestingly, differences in the psychosocial factors between seasonal and perennial allergies in the dataset have been observed, namely an association of anxiety with seasonal allergies, whereas depression was linked to perennial allergies [13]. There is evidence for an association of atopic diseases and attention-deficit hyperactivity disorder (ADHD). Even in unaffected siblings of ADHD patients, the risk of developing asthma, AD, AR, or any of these atopic diseases is increased with a relative risk between 1.1 and 1.19 [14]. Although an overall moderate disease burden and good adherence to the carrying of emergency medication was found in patients with insect venom allergy, several patients demonstrated borderline or significant anxiety and/or depression disorders [15]. Therefore, a regular assessment of psychological well-being to identify patients requiring psychological support is recommended [15].

Whether there is a link between asthma severity and lower urinary tract symptoms (LUTS) has been analyzed

in a cross-sectional study involving 101,848 males in Korea, which indeed found male asthma associated with LUTS that led the authors to conclude that an intensified urological diagnosis and treatment is needed in this patient group [16]. In a retrospective case-control study, allergic diseases showed an association with irritable bowel disease (IBD) with more frequent and severe symptoms of IBD, and serum total IgE correlated with gastrointestinal symptoms in atopic patients [17].

Identification of New Risk Factors and Disease Subgroups

Different allergic diseases co-occur in asthma and allergy patients, and multimorbidity is common across all age groups, producing an immense impact on disease severity, drug use, and costs, as shown in a study from Finland [18]. A novel approach to assess the incidence of pollen allergy has made use of Google Trends. By analyzing the use of certain queries, e.g., pollen, hay fever, and allergy, different seasonal patterns of pollen exposure in American and European countries have been identified [19]. The use of three terms, allergy, hay fever, and ragweed, allows the calculation of pollen exposure, and, in combination with pollen counts, can be used in epidemiological studies [20]. In patients allergic to cypress pollen evaluated over three consecutive seasons, a significant association between exposure to cypress pollens and allergic symptoms of the upper airways and conjunctiva, but not bronchial symptoms, was reported [21]. Peripheral blood eosinophilia occurring in the context of non-AR was identified as a risk factor for chronic rhinosinusitis with nasal polyps (CRSwNP) and CRSwNP morbidity [22]. Recently, a distinct phenotype of adult asthma associated with AR or allergic conjunctivitis and the prevalence of the IL13 rs20541A- allele has been described [23]. Severe chronic upper airway disease, defined as inadequate symptom control despite adequate pharmacologic treatment, correlates with polysensitization, but not asthma, and thus reflects the inadequate use of allergen-specific immunotherapy (AIT) [24].

A retrospective study on patients with eosinophilic granulomatosis with polyangiitis (EGPA), a systemic vasculitis associated with asthma, tissue eosinophilia, and anti-neutrophil cytoplasmic antibodies (ANCA) in 30–40%, showed a significantly higher ratio of ANCA positivity in patients previously treated with leukotriene receptor antagonists (odds ratio 6.42) [25]. Although a causality has not been proven, this observation should

stimulate further research on the action of leukotriene receptor antagonists, their effects on neutrophils, and a tailored treatment for ANCA-positive and ANCA-negative EGPA [25]. A recent study on EGPA revealed that even when the rheumatologic assessment according to the Birmingham vasculitis activity score and vasculitis damage index indicates no activity, sinonasal inflammatory processes may continue and should be monitored, including eosinophil numbers in nasal cytology [26].

As a risk factor for anaphylaxis in patients with immediate drug hypersensitivity reactions, for which non-steroidal anti-inflammatory drugs (NSAIDs; 56.9%) and β -lactams (34.7%) were the most common culprit drugs, parenteral usage of the drug and the presence of atopy were identified [27]. In children, NSAIDs are the second most frequent substances to cause hypersensitivity reactions that was found to occur more frequently in children with asthma than in controls [28]. Thus, NSAID intolerance should be evaluated in asthma patients [28]. The incidence of rash after aminopenicillin treatment in children with Epstein-Barr virus (EBV) infection seems to be lower than previously estimated. Out of 221 patients with EBV infection, 54.3% were treated with antibiotics and 41 (18.6%) developed a rash, of whom only 20 were treated with antibiotics, suggesting that both paraviral and drug hypersensitivity reactions may occur during EBV infection [29]. In clinical practice, distinguishing drug reactions with eosinophilia and systemic symptoms (DRESS) with and without infection can be challenging. A epidemiological biomarker study revealed that evaluating CRP and procalcitonin might be helpful in indicating concomitant infection [30]. Patients with common variable immunodeficiency have an increased prevalence of bronchial hyperresponsiveness and bronchial asthma, which is considered to be a non-atopic and non-eosinophilic type of asthma [31]. A literature review on the effect of partially hydrolyzed whey-based formula on growth and AD risk-reduction in the general infant population confirmed that it supports normal growth in infants, and may reduce the risk of AD in not fully breastfed infants from the general population, when compared to the use of cow's milk formula during the first 4–6 months of life [32].

New Insights in the Pathogenesis of Atopic Diseases

AD is a chronic inflammatory disease and is determined by a genetic predisposition characterized by an impaired skin barrier and a T-helper 2-predominant inflammation. An understanding of the pathogenesis has an im-

portant impact on the disease management. Restoration of the skin barrier is the main approach for treating and preventing AD. The anti-inflammatory therapy with immunosuppressive drugs is being complemented by novel targeted therapies, among which an anti-interleukin (IL)-4/IL-13 receptor antibody has been approved in several countries [33]. In addition to filaggrin mutations, polymorphisms in other genes encoding cornified envelope proteins such as cornulin and repetin have been found associated with AD [34]. Stress is known to cause relapses of inflammatory skin diseases such as psoriasis, for which an activation of the central and local hypothalamic-pituitary-adrenal axis systems has been postulated. Indeed, dexamethasone injected in mice increased the expression of keratinocyte growth factor by dermal mast cells resulting in a thickening of the epidermis [35]. The observation that the incidence of AD was inversely associated with the release of IL-10 from mononuclear cells in the cord blood of infants with fecal *Bifidobacterium* indicates a possible role of an impaired IL-10 production in response to microbial stimuli at birth in the pathogenesis of infantile AD [36].

AR, in particular when severe and associated with local eosinophil inflammation, was shown to affect mucociliary clearance in children, and thus may inhibit one of the most important protective functions of the airway [37]. Initial impaired lung function determined by exhaled nitric oxide was detected in patients with AR and eosinophilic chronic rhinosinusitis [38, 39]. Since chronic rhinosinusitis has been linked to taste receptor signaling, six single nucleotide polymorphisms in genes with known bitter tastant signaling function have been studied, and it could be demonstrated that a variation in an established G-protein component downstream of bitterant receptor signal transduction, GNB3 SNP rs5443, was associated with decreased GRK2 ubiquitination [40]. In order to further unravel the mechanisms of AIT, the expression of the epigenetic regulator Enhancer of Zeste homolog 2 (EZH2) in circulating myeloid dendritic cells (DCs) and plasmacytoid DCs was assessed and found to decrease over treatment [41]. This in vivo observation together with in vitro experiments suggests EZH2 plays a role in DC and T cell activation which is downregulated during AIT [41].

Asthma airway diseases are considered as T helper 2 responses, but in addition, allergic inflammation seems to be driven by group 2 innate lymphoid cells (ILCs), as ILC2 levels are elevated in the peripheral blood and correlate with the eosinophil numbers in patients with asthma and AR when compared to healthy controls [42]. IL-33 is known to initiate type 2 immune responses. Allergen inhalation chal-

lenge is followed by a significant upregulation of the IL-33 receptor ST2 on the surface of eosinophils derived from blood and sputum of mild asthmatics [43]. In line with this observation, IL-33 stimulation of eosinophils increases both ST2 membrane expression and IL-5 production in vitro, suggesting that IL-33 might be a novel therapeutic target [43]. The effects of different stimuli on dendritic cells have been studied using liquid chromatography-Fourier transform ion cyclotron resonance mass spectrometry, revealing that Th2 polarization is determined by metabolism and stress in addition to the immunological synapse between DCs and T cells [44]. A high expression of IL-25 and IL-33 receptors on the surface of basophils of patients with severe asthma has been detected and suggests a stimulation of basophils by epithelial-derived cytokines [45].

Activin-A has been shown to be highly expressed in mucosal tissue of patients with chronic upper airway disease, with nasal polyps being regulated by and regulating transforming growth factor (TGF)- β 1 expression and combined with TGF- β to enhance IL-5 expression [46]. This finding suggests activin-A must have proinflammatory properties [46]. The improved understanding of asthma pathogenesis has led to the identification of several subgroups which can be identified by clinical markers and/or biomarkers, including cytokines/chemokines and their receptors, eosinophilic inflammation, total and allergen-specific IgE, as well as genotypic features. These have recently been summarized [47, 48]. Sialic acid-binding Ig-like lectins (Siglecs) that are members of the Ig gene family are expressed on several kinds of immune cells contributing to the pathogenesis of asthma, including neutrophils, eosinophils, and natural killer cells, which could serve as targets for therapy [49].

Periostin has been detected in the airways of patients with both acute and chronic eosinophilic pneumonia correlating with high eosinophil and lymphocyte counts, and concentrations of IL-5, IL-13, and TGF- β 1, indicating a local expression and pathogenic role of periostin [50]. Periostin is produced by bronchial smooth muscle cells upon stimulation with IL-13 via the JAK/STAT6, ERK1/2, and PI3K/Akt pathways, implicating a role in asthma pathogenesis [51].

Elucidating the Role of the Innate and Adaptive Immune Systems

Mast cells, as innate immune cells that are distributed in nearly all tissues, are potent effector cells contributing to host defense and immunoregulation under physiolog-

ic and pathologic conditions. The spectrum of mast cell functions is broad, as is their role in tissue homeostasis and diseases, including allergy, angiogenesis, cardiometabolism, and tumor initiation [52]. For the purpose of differential diagnoses of mast cell diseases and evaluation of mast cell numbers, various staining techniques have been developed [53]. Recently, it has been shown that the R753Q Toll-like receptor (TLR-2) gene polymorphism present in the genotype 753Q variant of the TLR-2 gene increases the risk of mastocytosis more than 2-fold, and that of systemic mastocytosis more than 4-fold [54]. Chronic spontaneous urticarial (CSU) caused by *Helicobacter pylori* has long been a matter of debate. Recent findings point to the fact that upper gastrointestinal inflammation per se and independent of *H. pylori* infection is associated with CSU [55]. Healing of upper gastrointestinal erosions was accompanied by an improvement of urticarial symptoms indicating that an underlying inflammation rather than an immunological reaction affects urticaria [55]. Compared with controls, CSU patients were found to have elevated plasma levels of total nitric oxide, histamine-releasing factor (HRF), and HRF-reactive IgE [56, 57].

Recurrent angioedema (AE) without wheals is increasingly recognized as a clinical entity and a frequent cause of admission to the emergency room. Recent improvement in understanding the mechanisms leading to their pathogenesis resulted in the description of different AE phenotypes, knowledge of which is crucial for a better management of patients with AE [58, 59]. Hereditary AE (HAE) is a rare autosomal dominant disease characterized by episodes of swelling involving the gastrointestinal tract, airways, and/or skin due to mutations of the SERPING1 gene encoding C1-inhibitor resulting in a quantitative (HAE type I) or functional (HAE type II) deficiency of the protein. The correlation between the mutation pattern and the phenotype in a Turkish HAE cohort revealed large deletions and nonsense mutations associated with low levels of C1 inhibitor, while deletions and large deletions had the highest impact on reduced C1 inhibitor function [60]. Although early disease onset and low levels of C1 inhibitor function strongly affected the course of HAE, a direct correlation between mutation type and phenotype was not observed [60]. Another study reported that the carriage of KLKB1-428G/A, whether combined or not, with the functional F12-46C/T polymorphism correlates with the onset and disease course of HAE and may be used as a prognostic biomarker [61]. Interestingly, an ethnic variability in prevalence, clinical manifestation, and severity of HAE has been observed in

Korea compared with Western countries [62]. Increased circulating vascular cell adhesion molecules and endocan (also called ESM-1) in patients with HAE suggests an endothelial activation even in attack-free periods [63].

In order to study the effect of the microbiota on allergic diseases, bacteria-derived extracellular vesicles, known to play a role in interbacterial and human bacteria interaction, were analyzed in the urine of children with chronic rhinitis and AR and atopic asthma, revealing a dysbiosis in allergic children compared to healthy controls with distinct patterns in different disease groups [64]. The burden of allergic disorders in rural areas is reported to be low and inversely associated with helminth infections. In agreement, a preventive mass drug administration of albendazole for school children in Indonesia led to a significant reduction of soil-transmitted helminths, but increased the risk of being SPT positive to any allergen by an odds ratio of 3.04 [65].

A study aiming to investigate the early effects of subcutaneous immunotherapy with house dust mite allergen revealed cycles of expansion and contraction of Tregs and IgE+ B cells that occur with each subcutaneous immunotherapy injection, while the percentages of CD4+ and CD8+ T cells, NK cells, total B cells, and basophils remained constant [66]. As oral and sublingual immunotherapy have been reported to elicit eosinophilic gastrointestinal disorders, patients with these disorders should be followed up and, in the case of gastrointestinal symptoms, receive endoscopy [67].

Selective IgA deficiency is associated with heterogeneous genetic and immunologic abnormalities involving T and B cell function, cytokines and their receptors, apoptosis, as well as microbiota effects [68]. Despite the high prevalence of selective IgA deficiency, the pathogenesis and links to other primary immunodeficiency disorders are not completely understood [68]. Hyper-IgM syndrome is a rare primary immunodeficiency disorder characterized by low or absent serum IgG and IgA that predisposes for pneumonia and lower respiratory tract infection, and is associated with mutations of the CD40 ligand gene (68.5%), as well as activation/induction of the cytidine deaminase, lipopolysaccharide-responsive and beige-like anchor, nuclear factor-kappa B essential modulator, phosphoinositide-3-kinase regulatory subunit 1, and nuclear factor-kappa B subunit 1 genes. [69]. Common variable immunodeficiency is associated with increased susceptibility to infections and increased frequency of inflammatory and autoimmune diseases, for which alterations of the regulatory lymphocyte population such as decreased proportions of natural and in-

duced CD4+ Treg, induced CD8+ Treg, and Breg (CD19+ CD24high CD38high) might be contributing factors [70]. Notably, symptoms of asthma, rhinitis, and AD have been reported by 28/31 patients with primary immunodeficiency in whom sensitizations to aeroallergens as assessed by SPT are less frequent as compared to the general population [71]. Moreover, after chemotherapy, allergen-specific IgE levels decrease, but markedly less than B cell counts, suggesting that at least some allergen-specific IgE plasma cells survive chemotherapy [72].

A fraction of adults with autoimmune diseases have clinical diabetes that initially does not require insulin (latent autoimmune diabetes of the adult; LADA). Distinct polymorphisms of the PTPN22 gene clearly distinguished LADA from type 1 and type 2 diabetes mellitus [73]. By means of ophthalmological examination, standard automated perimetry, spectral-domain optical coherence tomography, and fundus perimetry, subclinical functional eye impairment was demonstrated in patients with systemic lupus erythematosus associated with kidney involvement, and Sjögren syndrome linked to hydroxychloroquine toxicity [74].

Linking Clinical Manifestation and Sensitization Pattern

The sensitization pattern in a population is determined by the exposure to environmental allergens and demographic factors, and thus has an impact on the management of allergic diseases, e.g., assembling a standard SPT panel. In an atopic population of eastern India, house dust mites *D. pteronyssinus* and *D. farinae*, pollen of *Cocos* and *Azadirachta*, as well as the mold *Alternaria* underlie most commonly elicited positive SPT reactions [75].

Component-resolved diagnostic tests allow the measurement of IgE antibodies to specific components of allergens, and thus provide detailed information on the sensitization pattern and cut-off levels correlating with allergic symptoms [76]. A real-life study revealed that the ImmunoCAP test provided the best results in patients with suspected allergy to nuts, wheat, other specific foods, and anaphylaxis, whereas the immuno-solid-phase allergen chip (ISAC) was most suitable in detecting oral allergy syndrome [77]. There is a geographical heterogeneity probably related to differences in pollen counts and genetic backgrounds. In Iceland, half of peanut-sensitized individuals are not sensitized to the major allergen Ara h 2, whereas sensitizations to Ara h 1, Ara h 3, and

Ara h 6 correlated with positive open peanut challenge [78]. In Spanish peanut-sensitized children, sensitization to Ara h 1 and Ara h 2 is more frequent in the group of allergic patients, while peanut-tolerant children lacked sensitization to Ara h 9 [79]. In patients with suspected buckwheat allergy, Fag e 3-specific IgE should be determined since these were demonstrated to predict positive oral food challenge tests and oral food challenge-induced anaphylaxis [80]. Grass-allergic children frequently show cross-reactivity to wheat, mainly Phl p 12 and cross-reactive carbohydrate determinants, while wheat-allergic patients have been found to be cosensitized to wheat-specific allergens derived from the gluten fraction [81].

Among individuals allergic to either hazelnut or walnut, a cross-reactivity of seed storage proteins of hazelnut, Cor a 14, and Cor a 9 with walnut Jug r 1 has been observed in 9/12 and 7/8 patients, respectively [82]. This observation suggests a potential increased risk of severe allergic reactions caused by cross-reactivity between 2S albumins and legumins [82]. Low-dose oral food challenge with hazelnut proved to be well tolerated and safe in pediatric hazelnut-allergic patients and provided clinically meaningful information on the tolerated amount of hazelnuts [83]. As risk factors for severe reactions to oral food challenges, previous anaphylaxis to the suspected food and older age have been identified [84]. Although rare, patients with buckwheat allergy tend to develop severe anaphylactic reactions upon food challenge [85]. The case of a mastocytosis patient with anaphylaxis after the ingestion of figs demonstrates the potential pitfalls of allergy diagnostics as, rather than fig, hymenoptera, i.e., *Blastophaga psenes*, antigen contamination was the suspected trigger [86]. In cat-sensitized patients with perennial AR, a cat allergy as assessed by a positive cat nasal challenge test can be predicted with a cat SPT wheal size of >6.5 mm with 71.11% sensitivity and 100% specificity [87].

In patients with rhinitis of suspected allergic origin but negative SPT, a nasal provocation test should be considered to identify a local AR [88, 89]. Therapy with oral corticosteroids even at low doses and in the short term might affect the accuracy of diagnosis as shown for eosinophilic chronic rhinosinusitis, resulting in a misdiagnosis rate of 15.9% [90]. Routine *Aspergillus fumigatus*-specific IgE screening for asthma patients has been recommended based on a study including 1,842 asthma cases, as this may significantly improve the diagnostic rate of allergic bronchopulmonary aspergillosis [91].

Since the sensitization profiles of patients with latex allergy have significantly changed over time, namely a de-

creasing frequency of positive SPTs correlating with a specific IgE to latex, a combination of patient history, SPT, and analysis of specific IgE is recommended to correctly diagnose latex allergy [92]. A monosensitization to Hev b 8 in grass pollen-allergic patients has no or little clinical relevance due to cross-reacting allergens, here Hev b 8 and Phl p 12 [93]. A further study reported false positivity to latex-specific IgE in ImmunoCAP analysis in 19% of patients with pollen allergy due to cross-reactive profilins and bromelain [94]. A diagnostic work-up in dental professionals confirmed the low rate of allergy to latex, and showed skin lesions to be associated with longer work experience, frequent glove changes, hand washing, and atopy [95].

Introducing Novel Diagnostic Methods

There are efforts to develop novel techniques that allow serum-specific IgE to be determined at the point of care. A nanofluid assay to measure five allergens achieved 81% agreement with a conventional test and an overall agreement based on clinical history, SPTs, and IgE measurements of nearly 95% [96]. The CAP-inhibition test was shown to produce the most accurate results in the evaluation of double sensitization, i.e., *Polistes* and *Ves-pula* species, and cannot be replaced by alternative tests such as SPT, molecular diagnostics, and determining Ves v 5/Pol d 5 [97]. The basophil activation test was proven as a diagnostic method alternative to skin tests based on the finding that values for the basophil activation percentage and mean stimulation index for CD203c expression with oxaliplatin were higher in patients with hypersensitivity reactions than in controls [98]. In patients with drug hypersensitivity reactions, the basophil activation test was shown to be effective in discriminating adverse drug reactions as it had a high specificity, but low sensitivity for antibiotics and NSAIDs, and thus may supplement the diagnostic work-up [99]. D-Dimer levels in plasma, which are elevated in patients with CSU and correlate with disease severity, may serve as biomarkers indicating clinical response to omalizumab therapy [100].

The atopy patch test with food allergens such as cow's milk, egg, wheat, and soy is a reliable diagnostic tool to evaluate food allergy-related skin symptoms in children [101]. With the development of novel matrices, a long-term application of placebo and verum food challenge tests for patients with non-immediate-type reactions to milk and raw egg at home is feasible and has been proven safe [102]. Compared to SPT, allergen molecule-based di-

agnostic testing allows a more precise prescription for immunotherapy followed by reduced combined costs for diagnosis and treatment [103].

Non-IgE-Mediated Food Hypersensitivity

In the era of fashion-driven gluten-free diets, the diagnosis of celiac disease (CD) and wheat allergy is challenging. A recent study reported a positive anti-tissue glutaminase IgA (tTG IgA) in 128 of 2,965 tested patients, but only tTG IgA levels 12-fold above normal correlated with CD. Specific IgE to wheat and tTG IgA values were negatively correlated [104]. CD is an autoimmune enteropathy triggered by the ingestion of gluten-containing cereals and has the global prevalence of approximately 1% [105]. Current screening strategies among pediatric populations include large-scale studies (CD mass screening) and studies performed on children in increased-risk groups. Alternatively, questionnaire-based surveys have been initiated that failed to provide an accurate assessment of CD [105].

Food protein-induced enterocolitis (FPIES) syndrome is a non-IgE-mediated food hypersensitivity that requires oral food challenge to confirm the diagnosis; these, however, can be risky and induce severe reactions. The application of a unique dose on 2 or 3 non-consecutive days instead of giving several doses during the same day can significantly reduce the number of moderate to severe reactions to fish [106]. In a Greek pediatric FPIES cohort, cow's milk and fish were the most commonly implicated foods [107].

Diagnosing Urticaria and AE

Threshold testing in patients with symptomatic dermographism, a subtype of inducible urticaria, is helpful for assessing disease severity and response to therapy. The newly developed total Fric score, which is a 4-grade rating score based on the results of the Fric test 4.0, was shown to correlate with the pruritus score, patients' global assessment score, dermatology life quality index (DLQI), but negatively with the physicians' global assessment and the urticarial control test [108]. Thus, the Fric test is considered a helpful tool for monitoring disease activity [108]. In patients with anaphylaxis, serum tryptase levels are significantly higher in patients with severe (grade IV) than those with mild to moderate (grade II-III) anaphylaxis, and may help to estimate the risk of further episodes [109]. As one of the criteria of the mast cell acti-

vation syndrome, the 20% + 2 formula, developed in 2012, has been validated in practice by independent groups and found to be a sound tool for measuring a clinically relevant increase in tryptase, independent of the baseline level [110]. An ABC of warning signs of HAE has been developed that should allow patients, family members, and medical staff to recognize early attacks of HAE that might otherwise be fatal [111].

Toward an Effective and Safe Drug Testing

Multiple drug hypersensitivity is an emerging syndrome that is characterized by long-lasting drug hypersensitivity reactions to different drugs as a consequence of massive T cell stimulation to multiple, structurally unrelated drugs with clinically diverse symptoms [112]. The clinical presentations, disease course, culprit substances, and pathomechanism, as well as the diagnostic tests and therapeutic management, have recently been reviewed [112]. Based on the observation that cross-reactivity between proton-pump inhibitors (PPIs) may occur, patients with suspected PPI hypersensitivity should be tested with both the culprit and alternative PPI using a thorough work-up, including skin test and, if negative, oral challenge [113].

In view of potential consequences, including adverse health and economic outcomes, a recent review highlighted the prevalence, diagnosis, and management of different types of antibiotic allergies in children and revealed a shift from the use of skin tests and, if negative, challenges to the use of challenge only [114]. An accurate diagnosis of penicillin allergy is supposed to reduce the rate and duration of hospitalizations and consequently the costs [115]. The practical value of a proper diagnostic work-up in patients with suspected immediate type allergy to β -lactams has again been demonstrated in several studies. By applying skin and challenge tests as well as serology, 85% were found to tolerate β -lactams [116]. Moreover, testing with various β -lactam antibiotics with different side chains is recommended in order to discriminate a selective allergy to β -lactams from an allergy to a side chain [116]. Among 90 children, a suspected ceftriaxone hypersensitivity was confirmed in 29%, notably by a high rate of positive skin tests in cases with immediate type reactions and anaphylaxis [117]. Cefazolin should be considered as a culprit drug of immediate severe allergic reactions in a perioperative setting. However, patients with IgE-mediated hypersensitivity reactions to cefazolin can tolerate amoxicillin and cefuroxime [118].

Evidence-Based Therapy and Real-Life Experience

According to current guidelines for CSU, antihistamines are the first-line therapy, at single to 4-fold dosages depending on the clinical response [119]. However, antihistamines, even upon up dosing, may not always control CSU and may induce adverse effects in children. This is why controlled trials have been demanded for the pediatric population [120]. In CSU patients not responding to antihistamines, omalizumab is indicated. Still, there is a small proportion of CSU patients in whom the regular dose of 300 mg every 4 weeks is insufficient and who require doses of 450–600 mg to achieve disease control [121]. However, by inhibiting CRTh2 with the antagonist AZD1981 and thus also type 2 cytokine production, eosinophil cationic protein release by eosinophils, and enhancement of allergen-induced basophil histamine release, a delayed positive effect on itch even more than on wheals has been reported in patients with CSU [122]. Following a 30-day oral supplementation of CSU patients with diamine oxidase, the enzyme that catabolizes and inactivates histamine, a disease improvement assessed by the UAS 7 score could be achieved in patients with low serum diamine oxidase baseline levels [123].

Anaphylaxis may present as a biphasic reaction. This is why patients should be observed over 6–12 h after resolution of an initial anaphylaxis symptom as recommended in the guidelines. According to a meta-analysis, observation times of 6 h and 8–12 h are sufficient to exclude recurrence of a secondary reaction in >95 and 98% of patients, respectively [124]. Adrenaline has been recommended as first-line therapy in anaphylaxis and should not be withheld because of potential side effects [125]. Since anaphylactic reactions in patients undergoing venom immunotherapy (VIT) are common, and emergency management of patients is not satisfactory, comprehensive standardized anaphylaxis education programs are required [126]. In HAE, a reduction of the frequency of AE attacks, daily severity, and the number of attacks requiring emergency treatment can be achieved by a prophylactic therapy with the nanofiltered C1 inhibitor Cinryze in both adult and pediatric patients [127].

AIT is the only allergy therapy that by inducing tolerance has long-term effects on clinical signs and symptoms; however, it is complex, time-consuming, and associated with risk of anaphylactic reactions. As an alternative route to subcutaneous, sublingual, and oral allergen application, intra-lymphatic immunotherapy has been shown to be effective and safe [128]. The major advan-

tages of intra-lymphatic immunotherapy are the short duration and the low allergen doses administered [128].

Based on recent studies, early food introduction in infants is recommended in order to induce tolerance and prevent food allergy [129]. A systematic review showed that an early introduction of egg was associated with a lower risk of egg allergy, and the nature and dose of egg protein exposure has an effect on preventing allergy [130]. In severe egg-allergic children who do not tolerate hard-boiled egg white, a low-dose oral immunotherapy is recommended, for which low-egg-allergen cookies can be used [131].

Cow's milk allergy (CMA) in infants requires the exclusion of cow's milk until tolerance is recovered. Factors associated with a rapid tolerance acquisition are non-IgE-mediated CMA and feeding with casein hydrolysate together with *Lactobacillus rhamnosus* GG, whereas patients with IgE-mediated CMA and those receiving casein hydrolysate without *L. rhamnosus* GG recovered later [132]. According to a recent randomized study, tolerance to cow's milk can be achieved upon oral immunotherapy with a partially hydrolyzed formula, whereas an extensively hydrolyzed cow's milk protein-based formula failed to increase the threshold of tolerated cow's milk protein [133]. The persistence of CMA was determined by the history of anaphylaxis and high milk-specific IgE levels [134]. In Japanese children with wheat allergy, the rate of tolerance acquisition is 66% at the age of 6 years. Risk factors for persistent allergy are a history of anaphylaxis to all foods, including wheat, and high levels of wheat- or ω -5 gliadin-specific IgE antibodies [80]. Upon oral immunotherapy with peanut allergen in patients with anaphylaxis to peanut, desensitization can be achieved by 8 months with a rate of sustained unresponsiveness of 68% after 2 years [135]. Food processing may have an immense effect on the immunogenicity of food, as shown for soybean allergens that are very resistant to heat and only lose their capacity to bind to IgE upon intense combined heat and pressure processing, and for peanut allergen with Ara h 3 internalization by DCs [136, 137].

AIT in patients allergic to *D. pteronyssinus* is equally effective, whether in the presence or absence of cross-reactivity to *Blomia tropicalis* [138]. Interestingly, during AIT with *D. pteronyssinus* extract, an increase of IgG4 levels cross-reactive to *B. tropicalis* have been detected [138]. SLIT with *D. farina* drops in children with AR confirmed the long-term effects and significantly reduced clinical signs and symptoms after 2 years of therapy with a sustained effect over 5 years. However, clinically sig-

nificant worsening during the 6th and 7th year in the patient group with polysensitization was observed [139].

For patients with seasonal AR, a novel combination therapy with azelastine hydrochloride and fluticasone propionate in a single spray was shown to be superior over azelastine monotherapy as assessed by severity scores and an improvement of patients' quality of life [140]. The response of eye irritation following a positive conjunctival provocation test to liposomal eye spray, a non-pharmacological treatment, is similar to that of antihistamine eye drops [141]. In patients with perennial AR, both triamcinolone acetonide and fluticasone propionate intranasal sprays showed similar efficacy and safety profiles [142]. A further study proved the efficacy of resveratrol, a natural, non-flavonoid polyphenol, in adult patients with AR and reported a significant reduction of symptoms, acting similar to budesonide, which was accompanied by a decrease of IgE, IL-4, tumor necrosis factor- α , and eosinophil levels in blood [143]. In children, buffered hypertonic saline was effective in coping with seasonal AR symptoms [144]. Symptoms of dry eye with AR can be treated successfully with nasal steroid therapy, without affecting the intraocular pressure [145]. After endoscopic sinus surgery in patients with NSAID-exacerbated respiratory disease, both nasal steroids (mometasone) and antileukotrienes (montelukast) have similar effects in terms of general well-being, state of pathological changes, and olfactory disorders, whereas a combination of the two is not superior [146]. Sublingual immunotherapy significantly improved symptom severity in patients with Japanese cedar pollen AR, and was remarkably effective in the late pollen season [147]. In asthma patients, the long-term application of omalizumab resulted in a significant reduction of the asthma exacerbation rate, hospitalization rate, and improvement of asthma control test results after 1 year, with a sustained effect over 5 years [148].

The evaluation of VIT outcome in patients exclusively with bee venom allergy demonstrated that VIT can be performed safely and efficiently. A c-kit mutation was identified as the only significant risk factor for VIT-induced systemic reactions upon rush protocol [149]. Female gender, c-kit mutation, but not tryptase level, and severe reactions to the index sting were found to be risk factors for recurrent and severe systemic reactions [149]. The finding that IgG serum levels and the IgG/IgE ratio increases during VIT in most patients, and a high IgG/IgE ratio correlates with low skin test reactivity after ≥ 3 years of VIT, makes IgG/IgE an interesting candidate as a biomarker for VIT efficacy [150].

Fluoroquinolones are broad-spectrum antimicrobial agents with significant immunomodulatory effects in addition to their antimicrobial properties. Bronchial asthma and COPD patients with an acute exacerbation and fever were shown to profit from therapy with garenoxacin added to the standard care [151].

A retrospective study on rapid drug desensitization with chemotherapeutics such as platins, taxanes, doxorubicin, irinotecan, and etoposide reported a safe and effective application of a 12- or 16-step protocol [152]. In patients with an acute coronary syndrome and a history of NSAID hypersensitivity, challenge and/or desensitization are recommended according to a recently developed protocol using increasing doses of acetylsalicylic acid up to a cumulative dose of 315 mg, a procedure that can be done within 2 h and has been proven to be well tolerated [153].

Outlook

The scientific data of recent years provide further pieces in the puzzle of understanding diseases characterized by imbalances of the immune system. Still, there is a need to discover the exact pathogenic impact of genetics and environment on disease mechanisms in order to provide effective preventive actions, adequate diagnostic procedures, including monitoring with biomarkers, and novel treatment strategies for our patients.

Disclosure Statement

The author has no conflicts of interest to declare.

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