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Recent Advances in Clinical Allergy and Immunology

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Abstract
Allergic diseases are of great concern because of their high prevalence, which is still rising in several regions, their impact on patients' physical and psychological health, the huge burden they place on patients' quality of life, as well as the socioeconomic consequences that they cause. Recent research has provided new data on both genetic and environmental risk factors of atopic/allergic diseases. The application of new technologies such as "omics" has allowed a better understanding of the pathogenesis and has helped with the identification of therapeutic targets. Immense progress has been made in developing and applying novel, targeted therapies, for example for asthma and urticaria. Intensive efforts are being made to find biomarkers that help to classify patients, to identify their potential responsiveness to specific therapies, and to monitor the disease severity. Based on recent insights in the pathogenesis of food allergy and drug hypersensitivity, novel strategies for diagnostics, allergen avoidance, and induction of tolerance have been developed. Here, we summarize important findings in the field of clinical allergy and immunology with a special focus on asthma, allergic rhinitis, atopic dermatitis, food allergy, urticaria, angioedema, and drug hypersensitivity.

Introduction

Allergic diseases are common, may seriously affect patients' physical and psychological health and thus exert a huge burden on patients' quality of life as well as on society as a whole. Recent epidemiological studies indicate that the prevalence of such diseases is still increasing in several countries, and reveal new risk factors for the development of atopic/allergic diseases. With the better characterization of the diseases, in particular by applying new technologies such as "omics," it has become obvious that various subgroups exist among these disease entities, for example asthma, allergic rhinitis, atopic dermatitis (AD), and angioedema (AE). Such findings are important

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in view of the development and application of novel, targeted therapies. Intensive efforts are being made to find biomarkers that can help to classify patients, to identify their potential responsiveness to specific therapies, and to monitor the disease severity. In the last few years, new therapies have been studied and approved, such as omalizumab for asthma and urticaria, and these, having now become real-life experiences for patients and clinicians, are providing long-term data. This review summarizes important findings in the field of clinical allergy and immunology.

Toward New Therapies for Asthma

A steady increase in the prevalence of physician-diagnosed asthma, allergic rhinitis, and AD among children aged 6–14 years was reported for Turkey between 1994 and 2014 [1]. The incidence of adult-onset asthma in a population-based cohort in Italy was 4.6% and, interestingly, was not associated with current smoking, though it was greater in ex-smokers compared to never-smokers [2]. In a Brazilian cohort, allergic and nonallergic forms were found to present distinct phenotypes, such as age of onset, rate of intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs), and differing relevant genotypes as shown for HLA class I and II [3].

Asthma is a chronic inflammatory disease that comprises various subgroups with distinct clinical phenotypes, pathomechanisms, and responsiveness to treatment. In order to classify asthma patients and assign them to specific, targeted therapies, biomarkers, and biomarker profiles – for example cytokines involved in asthma pathogenesis – periostin as a marker of eosinophilic inflammation that is IgE specific to certain allergens has become very important [4]. Furthermore, the expression of the interleukin (IL)-33 receptor ST2L on eosinophils, which increases significantly at 24 h postallergen inhalation in allergic asthmatics, might serve as a biomarker and is considered a therapeutic target for asthma [5]. The presence and levels of epithelium-derived cytokines in exhaled-breath condensate have been studied in patients with chronic asthma in order to identify biomarkers for asthma severity. Although thymic stromal lymphopoietin (TSLP) and IL-33 could be detected, confirming their role in asthma pathogenesis, their levels of expression failed to discriminate between controlled and uncontrolled asthma [6].

Respiratory allergy to house dust mites is very common, and thus the recent introduction of sublingually administered allergen immunotherapy tablets (SLIT-tablets) inaugurates a new era for immunotherapy. Despite the fact that biologic material is used to produce the allergen extracts, the standardized production process guarantees high quality and minimal variance between batches [7]. Omalizumab, which has been approved for the treatment of asthma, has excellent short- and long-term effects on asthma outcomes, such as asthma exacerbation and hospitalization rates, as well as with an asthma control test over a period of 5 years [8]. Targeting eosinophils by blocking IL-5 or its receptor is a novel approach for asthma treatment. Benralizumab, an anti-IL-5 receptor antibody, has been demonstrated to significantly reduce the number of asthma exacerbations and to increase the forced expiratory volume in 1s, FEV_1, in an Asian population [9]. Recent observations demonstrate a role for the IL-25/IL-25 receptor axis in asthma, thus also identifying this as a novel therapeutic target [10].

Characterization of Subgroups of Allergic Rhinitis

According to a meta-analysis of 67 cross-sectional studies, the male predominance for development of rhinitis in childhood changes towards a female predominance in adolescence worldwide, except in Asia [11]. In Japanese students, both seasonal and, in particular, perennial allergic rhinitis are significantly associated with a current wheeze [12]. A cross-sectional, observational study investigating real-world practice patterns for allergic rhinitis, asthma, chronic obstructive pulmonary disease, and rhinosinusitis in India, Korea, Malaysia, Singapore, Taiwan, and Thailand provided regional and country-specific information and suggested different practice patterns between specialists and general practitioners, and highlighted the substantial disease burden [13].

An epidemiological survey performed in six cities in France illustrated different sensitization patterns to indoor and outdoor allergens, correlating with geographical location, climate, and environmental exposure [14]. Because of the climate changes and urbanization, ragweed has spread worldwide and has become an important allergen, causing rhinitis and asthma. Immunotherapy to ragweed pollen has been conducted for over 100 years; however, new technologies, such as the application of recombinant allergens, are needed to improve efficacy [15]. Moreover, using new media and building up networks will help to raise awareness and spread information, both to health professionals and to patients [16]. In order to standardize measures of outcome with conjunctival provocation tests, the use of a new scoring protocol, including

the items itching, irritation, tearing, and redness supported by an objective photodocumentation, has been validated [17].

Among grass pollen-allergic children with pollinosis, a subgroup showed a simultaneous sensitization to wheat. Interestingly, wheat sensitization was caused by both cross-reactivity and cosensitization to wheat-specific allergens, and was associated with allergy to staple foods other than wheat [18].

As the nasal provocation test with grass pollen and house dust mites was found to be positive in 25% of non-allergic rhinitis patients, it is strongly recommended to consider and diagnose a local allergic reaction (LAR) [19]. LAR could be confirmed among 25% of adult and 3.4% of pediatric patients with perennial nasal allergy symptoms but a negative skin prick test and an absence of specific IgE antibodies [20, 21]. Whereas house dust mites are the most common cause of LAR in Caucasians, pollens were identified as an important trigger of LAR in China [22].

The clinical relevance of pollen sensitization is mainly determined by major allergens and not by panallergens such as profilin and polcalcin [23]. Chronic allergic sinusitis has been associated with allergy to aeroallergens; however, over 80% of patients with chronic sinusitis are also sensitized to food allergens though without any difference between the groups with and without nasal polyps [24]. In eosinophilic chronic rhinosinusitis (ECRS) the inflammation extends to the lower airways, as indicated by elevated FeNO, and endoscopic sinus surgery may improve both ECRS and pulmonary dysfunction [25]. It is noteworthy that, upon chemotherapy, allergen-specific IgE levels significantly decrease, but do not disappear, suggesting that some plasma cells survive, still producing IgE [26].

Saline nasal irrigation with buffered hypertonic saline as an add-on therapy improves both clinical signs and quality of life in children with seasonal allergic rhinitis and is superior to normal saline solution [27]. Symptoms of dry eyes associated with allergic rhinitis improve upon intranasal corticosteroid therapy, while the intraocular pressure is not affected [28].

Understanding the Pathogenesis of Atopic Dermatitis

Based on novel insights in the pathophysiology of AD, recently developed anti-inflammatory drugs have been designed to specifically target components of the Th2 immune reaction, e.g., IL-13, the IL-4/IL-13 receptor, TSLP, JAK/STAT signaling, CRTH2, and IgE [29]. AD lesions are frequently located in the flexural folds suggesting sweat as a likely trigger. Indeed, skin prick tests to autologous sweat were positive and weakly positive in 38 and 34%, respectively, and correlated with clinical severity, total and specific IgE levels, and sweat tryptase activity [30]. In order to identify biomarkers for AD, stratum corneum tape stripping was applied as a minimally invasive approach for studying local levels of immunomodulatory molecules. CCL17 (TARC) and IL-8 significantly decreased upon therapy in parallel with disease severity [31].

A subgroup of children with AD develop food allergy. Recently, distinct microbial signatures discriminating between ADs with and without food allergy have been identified [32]. The atopy patch test is often used to diagnose food allergy in AD children. A recent study using a freshly prepared puree of cow's milk, egg yolk, egg white, and soy, provided high sensitivity and specificity as well as positive and negative predictive values, illustrating that the atopy patch test is a valuable diagnostic test for food allergy in patients without specific IgE [33]. A recent literature review investigating the efficacy and safety of a partially hydrolyzed whey-based formula in the general population concluded that it supports normal growth in infants, and may reduce the risk of AD in infants who are not fully breastfed as compared to infants receiving a cow's milk formula during the first 4–6 months of life [34]. Another study correlated 25-hydroxyvitamin D levels in umbilical cord blood and serum of infants with the development of allergic sensitization and diseases in early childhood. The authors found no association, thus, the discussion on the role of vitamin D in allergy remains controversial [35]. Unfortunately, exact data on the frequency and role of comorbidities are rare. A systematic review evaluating the association between allergies and hypercholesterinemia did not find conclusive results due to the heterogeneity of studies as well as lack of cross-sectional and prospective studies [36].

Improving the Diagnosis and Treatment of Food Allergy

In a cross-sectional study using a stepwise approach with questionnaires, food allergy was reported to occur in 10.8% of adults, of whom 1.0% were considered to have a positive food allergy diagnosis with reactions to fruits, followed in frequency by reactions against cow's

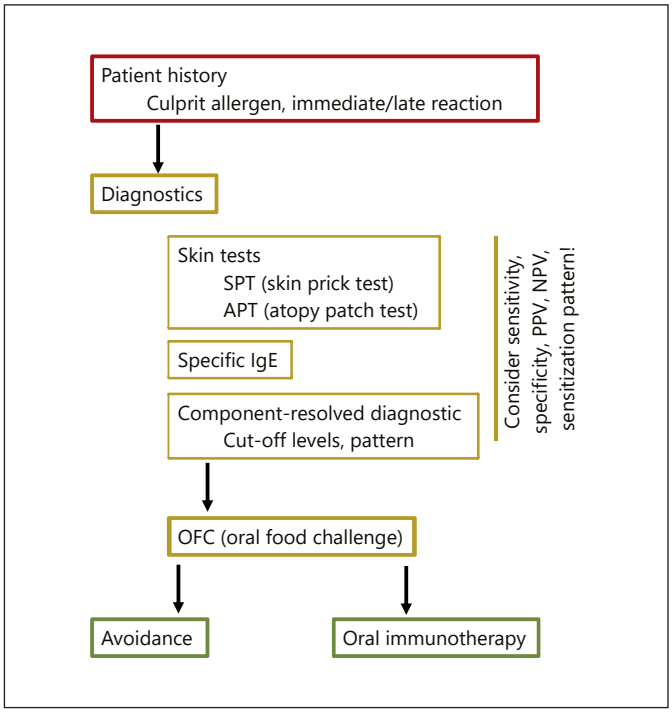

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Fig. 1. Management of food allergy: scheme of diagnostic procedures and therapy.

milk, shrimp, pork, and vegetables [37]. Data for a birth cohort indicate a 2.4% frequency of food allergy as confirmed by oral food challenge (OFC) for infants during the first year of life [38]. In order to study the association between milk and egg allergies and HLA polymorphisms, a bioinformatics approach was applied that mimicked the enzymatic degradation of food allergens and evaluated their binding affinity to DR and/or DQ molecules. Three susceptibility loci for milk and four for egg allergies, as well as four protective alleles for milk allergy, were identified [39].

Cow's milk is the major cause of food allergy in children [38]. For children with cow's milk allergy, amino acid formulas or extensively hydrolyzed formulas should be prescribed as recommended by international guidelines [40]. The risk of developing IgE sensitization to cow's milk has been associated with the duration of breastfeeding and isolated doses of formula feeding in hospital, especially after caesarian delivery [41]. Most children with food allergy develop tolerance, as shown for cow's milk (17/20) and hen's eggs (14/17), by the age of 2 years [42]. Risk factors for a persisting allergy to cow's milk or wheat include having a history of anaphylaxis and high food allergen-specific IgE levels [43, 44].

In order to provide exact dietary recommendations for patients with egg allergy, skin prick tests and measurements of specific IgE should be complemented by OFC tests with raw and heated egg white [45]. Oral immunotherapy with low doses of egg was reported to be effective and safe, and to result in a sustained tolerance in children [46, 47]. Sesame seeds (*Sesamum indicum* L.), buckwheat, and cashew nuts are rare allergens, but all may trigger severe allergic reactions; hence, the indications for any OFC tests should be carefully considered [48–50]. The characterization of Dutch patients with sesame allergy revealed a 14-kDa protein identified as oleosin (Ses i 4 and/or Ses i 5) as the major allergen and, furthermore, the possibility of a cross-reactivity of sesame with various tree nuts [48]. Indicators for a shrimp allergy are high levels of IgE to rPen a 1 and rDer p 10; the presence of a house dust mite-induced asthma and simultaneous IgE to Der p 1, 2, and 10 might help to distinguish between subjects with shrimp allergy and those that are sensitized but tolerant [51].

OFC is the diagnostic gold standard (Fig. 1). It should be considered that OFC tests bear the risk of severe allergic reactions, for which a history of anaphylactic reactions and older age are considered risk factors [52]. Since serum IgE levels to Ara h 2 have both high negative and positive predictive values, the number of OFC needed in suspected peanut allergy can be reduced [53]. In peanut-allergic patients from China, Ara h 9, a nonspecific lipid transfer protein, was identified as a major allergen [54]. Successful oral immunotherapy in children with an anaphylactic peanut allergy has been reported, with all children having achieved desensitization after 8 months, and 15 out of 22 patients maintaining a sustained unresponsiveness after 2 years [55].

In acute reactions of food protein-induced enterocolitis syndrome, an increased expression of CD69 on eosinophils has been noted, though the absolute eosinophil counts in the peripheral blood were not increased, suggesting CD69 as a marker for systemic events in the disease [56]. If patients on oral or sublingual immunotherapy develop gastrointestinal symptoms, they should be evaluated by endoscopy for eosinophilic gastrointestinal disorders [57].

Unraveling Urticaria

Omalizumab, an anti-IgE antibody, is recommended for the therapy of chronic spontaneous urticaria (CSU) refractory to antihistamines used even at 4-fold doses

Table 1. Warning signs for recognizing hereditary angioedema [74]

A	Angioedema
B	Bradykinin mediated
C	C1 inhibitor deficiency
D	Distress factors
E	Epinephrine nonresponsiveness
F	Family history
G	Glottis/gastrointestinal edema

[58]. The real-life experience of omalizumab efficacy shows a complete response in 85 and 60% of patients started on 300 and 150 mg, respectively, and a high safety profile [59]. Upon omalizumab therapy, a decrease in plasma D-dimer levels that had been elevated in 59% of CSU patients at baseline has been noted in responders [60]. CSU patients, in particular those with low plasma D-dimer levels, may benefit from autologous whole-blood injections as an add-on therapy to antihistamines [61]. Patients with low levels of diamine oxidase (DAO), an enzyme that catabolizes and inactivates histamine, slightly improve upon a supplemental therapy with DAO [62].

Despite the fact that coagulation is enhanced in chronic urticaria, the data on the role of platelets in the pathogenesis of CU are limited and conflicting [63]. As blood levels of NO_x and nitrate are significantly higher in CSU patients compared to healthy controls, and correlate with disease activity, a pathogenic role of nitrosative stress has been suggested [64]. A recent study reported a frequent association of CSU with upper gastrointestinal inflammatory disorders with and without *Helicobacter pylori* infection, and an improvement of urticaria in parallel with a successful treatment of the gastrointestinal disorder [65]. In India, *H. pylori* infections, which are mainly asymptomatic, are also frequent in CSU patients; however, the implications for disease course and severity are not clear [66]. Parasites were detected in 10% of children with CSU, of which half responded to an antiparasitic therapy [67].

In order to identify a genetic predisposition to NSAID-induced urticaria/AE, the presence of single-nucleotide polymorphisms in TSLP, IL7R, and TSLPR was investigated, but these were found not to be associated with the disease [68]. Based on the observation that CSU may be associated with a concomitant IgA deficiency (IGAD), a screening for IGAD- and IGAD-associated autoimmune diseases in CSU patients has been recommended [69]. High CD63 values upon basophil activation test have been recognized in children with CSU correlating with disease severity and possibly discriminating CSU from physical urticaria [70]. Acute urticaria has been reported more often in asthma patients (23%), mainly associated with seasonal asthma exacerbations, compared to 2% in healthy controls, whereas patients with CSU do not show an increased incidence of asthma [71].

The Diagnostic ABC for AE

AE without wheals has long been classified as either hereditary or acquired. Recent research has provided evidence that there is a heterogeneity of pathogenesis and phenotypes that allows a classification of subgroups, the establishment of diagnostic algorithms, and also has implications for treatment [72]. The characterization of patients with recurrent AE without urticaria reveals distinct subgroups based on clinical data and complement screening [73]. In order to diagnose and correctly treat hereditary AE (HAE) to avoid fatalities, an "ABC" for the warning signs of HAE has been developed: A = AE, B = bradykinin, C = C1 inhibitor, D = distress factors, E = epinephrine unresponsive, F = family history, and G = glottis/gastrointestinal edema (Table 1) [74].

Still, the etiology of AE is often difficult to determine, although this may sometimes be essential in emergency situations. A comparison of biomarkers revealed no differences in complement C1 and C4, but peaks of D-dimer levels during attacks and higher circulating VE-cadherin levels in patients with bradykinin- or histamine-mediated AE compared to those with abdominal pain of other causes, have been detected [75]. A shortened activated partial thromboplastin time is more frequently observed in patients with AE due to C1-INH deficiency compared to patients with various forms of AE with normal C1-INH [76]. Since blood levels of endocan and vascular cell adhesion molecules are increased in HAE patients even in attack-free periods, they are considered as markers for endothelial activation and might be able to serve as diagnostic markers [77].

In view of the large heterogeneity in the clinical presentation of hereditary AE due to C1 inhibitor deficiency (C1-INH-HAE), functional polymorphisms of the KLKB1 gene encoding plasma kallikrein and the F12-46C/T polymorphism were studied and showed that carriers of the G-allele of the KLKB1-428G/A polymorphism exhibited a significantly delayed disease onset by 4 years, while carriers of both the KLKB1-428G/A and the F12-46C/T polymorphisms displayed an 8.8-year delay in dis-

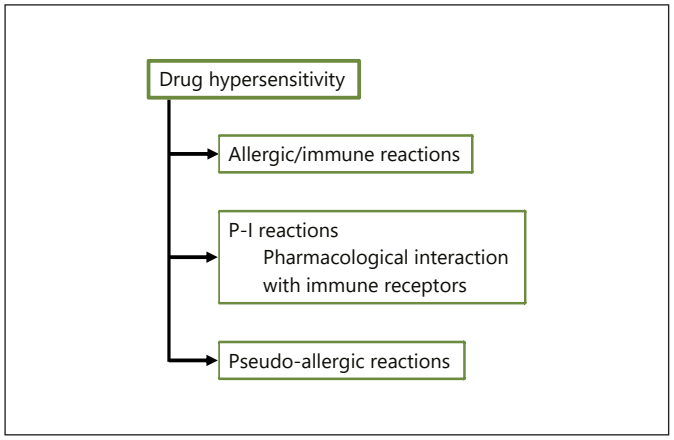

Fig. 2. Pathomechanisms of drug hypersensitivity [81].

ease onset and a 64% lower probability of needing long-term prophylactic treatment [78]. In addition, ethnic differences have been detected, indicating a lower prevalence of HAE and involvement of the gastrointestinal tract in Asia as compared to Western countries [79].

Supplementation of C1-INH has been shown to be effective in coping with and preventing attacks in HAE patients. Recently, the efficacy and safety of Cinryze, a nanofiltered human plasma-derived C1-INH, has been proven in children with HAE [80].

Drug Hypersensitivity: The Triad of Pathomechanism, Diagnostic Progress, and Management

Enormous progress has been made in understanding drug hypersensitivity. Three distinct ways by which stimulation of immune or inflammatory cells associated with typical clinical manifestations, time of appearance, dose dependence, predictability, and cross-reactivity have been identified: (a) an allergic/immune reaction; (b) pharmacological interaction with immune receptors (P-I reactions), and (c) pseudo-allergic reaction (Fig. 2) [81]. Multiple drug hypersensitivity is characterized by long-lasting hypersensitivity reactions to different drugs as a consequence of a massive T cell stimulation that first presents with exanthema or drug rash with eosinophilia and systemic symptoms, while upon the second stimulus, erythroderma, Stevens-Johnson syndrome/toxic epidermal necrolysis, hepatitis, and agranulocytosis may develop [82].

In patients with suspected allergy to amoxicillin, skin tests for determinants of amoxicillin and amoxicillin-clavulanate, in addition to major and minor penicillin determinants, are recommended in order to avoid false negative tests, and thus to decrease the need for oral provocation tests [83]. In children with an EBV infection a skin rash developed in 18.6%, of whom 50% were treated with antibiotics. A hypersensitivity reaction to aminopenicillin could be confirmed in 30–50% by drug provocation tests and re-exposure, respectively [84]. Higher comorbidity rates together with longer hospitalization stays have been noted in children with a penicillin allergy label; however, whether this is a cause or a consequence remains unclear [85].

Despite the high incidence of suspected non-β-lactam (NBL) hypersensitivity, the frequency of confirmed hypersensitivity is low, this being the reason why a detailed history should be taken from patients with suspected NBL hypersensitivity; furthermore, drug provocation tests should be performed in patients without contraindications [86]. NSAIDs are the second most frequent drug type to cause hypersensitivity reactions in children, these occurring mainly in children with asthma at a frequency of 1% [87].

Hypersensitivity reactions to NSAIDs, in particular to acetylsalicylic acid, are commonly reported; however, they can be confirmed in only 21% of patients. Clinical presentations are urticarial/AE or anaphylaxis [88]. In the case of NSAID hypersensitivity, those patients requiring dual antiplatelet therapy because of acute cardiovascular events might have to be diagnosed immediately and/or desensitized. A recently published algorithm provides best practice recommendations and has been proven feasible in establishing a safe administration of acetylsalicylic acid in cardiovascular patients with NSAID hypersensitivity with skin and/or respiratory involvement [89].

Pyrazolones are the most common causes of single NSAID-induced hypersensitivity and present as immediate reactions with urticaria/AE and anaphylaxis (60%), or as delayed hypersensitivity reactions such as maculopapular exanthema. A combination of diagnostic procedures including skin tests, basophil activation test, and drug provocation have been recommended to verify or exclude metamizole hypersensitivity [90]. In agreement with this conclusion, acetaminophen, the most commonly used antipyretic in children, should be considered as a possible cause of both immediate, most likely IgE-mediated, and nonimmediate hypersensitivity reactions [91].

The neuromuscular blocking agent rocuronium may cause IgE-mediated anaphylaxis as well as non-IgE-mediated hypersensitivity reactions that can be reversed by sugammadex, suggesting a non-IgE-mediated MRG-

PRX2- (Mas-related G-protein-coupled receptor member X2) triggered mast cell degranulation induced by rocuronium [92]. In cases of rare, immediate-type reactions to heparins that can be identified by skin prick testing, alternative therapies with unfractionated heparins or fondaparinux have been recommended [93].

When used as a tool to diagnose anticonvulsant drug hypersensitivity, the lymphocyte transformation test has a high specificity but a low sensitivity, and provides the most valuable results for the diagnosis of carbamazepine and phenytoin hypersensitivity [94]. A retrospective analysis of hypersensitivity reactions to proton pump inhibitors showed lansoprazole to be the most frequently implicated drug, followed by pantoprazole, esomeprazole, rabeprazole, and omeprazole, as well as anaphylaxis being the most frequent manifestation [95]. Since cross-reactions among proton pump inhibitors may occur, alternative drugs should be included in the diagnostic workup [95]. Rapid desensitization in patients with drug hypersensitivity to biologics, such as rituximab, infliximab, cetuximab, and trastuzumab, for which a detailed protocol has been developed, has been documented as safe and effective [96].

Identifying and Managing Anaphylaxis

As the main causes of anaphylaxis, food, drugs – most commonly NSAIDs – and insect bites have been identified, with 15% remaining idiopathic. Food allergy occurred more often in children, while drug anaphylaxis was more common in adults. There was an age-dependent shift of clinical presentations with gastrointestinal symptoms in infants and young children, respiratory symptoms in schoolchildren and adolescents, and cardiovascular symptoms in adults [97]. A cross-sectional study revealed symptoms of sting reactions in 13% of the overall population, of which half had systemic reactions. Interestingly, while a sensitization to venom was found in 15% of the population, only 31% of these had reacted to stings, while only 38% of those with sting reactions had IgE to venom. Surprisingly, no increased rate of reaction to stings was found in individuals with serum tryptase above the normal range [98].

Retrospective analyses of the use of epinephrine in anaphylaxis demonstrated a low rate of side effects that were usually mild and transient, and thus do not justify a restriction of adrenaline use in anaphylaxis [99]. Furthermore, underuse, inappropriate IV bolus use, and overdose were identified as major problems with epinephrine use, emphasizing the importance of training for professionals and education for patients [100].

Outlook

Over recent years, research has provided immense progress in understanding the pathomechanisms of allergic diseases and has unraveled new therapeutic approaches. With the development of novel therapies, of which some have already been approved, we face a new era of disease management and, with that, probably a modification of the expected course of diseases. Still, there are a number of unmet needs, for example in understanding the role of genetics and its interaction with the environment, monitoring disease severity, and response to treatment, and for preventing allergic diseases.

Disclosure Statement

The author has no conflicts of interest to declare.

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