

REVIEW ARTICLE

Update on skin allergy

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Abstract

Skin diseases with an allergic background such as atopic dermatitis, allergic contact dermatitis, and urticaria are very common. Moreover, diseases arising from a dysfunction of immune cells and/or their products often manifest with skin symptoms. This review aims to summarize recently published articles in order to highlight novel research findings, clinical trial results, and current guidelines on disease management. In recent years, an immense progress has been made in understanding the link between skin barrier dysfunction and allergic sensitization initiating the atopic march. In consequence, new strategies for treatment and prevention have been developed. Novel pathogenic insights, for example, into urticaria, angioedema, mastocytosis, led to the development of new therapeutic approaches and their implementation in daily patient care. By understanding distinct pathomechanisms, for example, the role of IL-1, novel entities such as autoinflammatory diseases have been described. Considerable effort has been made to improve and harmonize patient management as documented in several guidelines and position papers.

Over the last years, an immense number of studies investigating allergic skin diseases have been published. Here, we summarize and sort recent papers on the epidemiology, pathogenesis, and management of atopic dermatitis (AD), urticaria, angioedema (AE), mastocytosis, allergic contact dermatitis (ACD), and drug hypersensitivity. We will also present newly recognized diseases such as autoinflammatory diseases (AID), IgG4-related diseases, and mast cell activation syndrome (MCAS).

The better pathogenic characterization of patient subgroups among well-defined diseases and the identification of novel entities have an important impact on the disease management and pave the way for an individualized treatment. The primary aim of our update was to rather touch novelties

in research and clinical management of allergic skin diseases in order to raise interest and stimulate further reading than provide a comprehensive review.

Atopic dermatitis

Atopic dermatitis, a heterogeneous disease

Atopic dermatitis (AD) is a common chronic inflammatory skin disease presenting with heterogeneous clinical phenotypes that are determined by distinct genetic and epigenetic dispositions, resulting in a spectrum of endophenotypes (1). In 60% of patients, AD starts before the age of 6; in 18%, the onset is after the age of 20 (2). The heterogeneity of AD becomes apparent in different patterns of onset and natural disease course associated with distinct clinical features, variable risk of concomitant allergic diseases and food intolerance, and varying impact of psychic factors on symptoms (2). Recently, a number of studies investigating nonallergic comorbidities of AD have been published (3). Patients with AD have an increased risk of developing attention deficit/hyperactivity disorder (ADHD), whereas no association was found between AD and malignancies, diabetes, or multiple sclerosis (3). Although elevated total immunoglobulin (Ig)E levels are a characteristic feature of both AD and hyper-IgE syndrome, the pattern of IgE

Abbreviations

ACD, allergic contact dermatitis; AD, atopic dermatitis; AE, angioedema; AID, autoinflammatory disease; cADR, cutaneous adverse drug reaction; EET, eosinophil extracellular trap; Ig, immunoglobulin; ILC, innate lymphoid cells; IL, interleukin; iNKT, innate natural killer T cell; MCAS, mast cell activation syndrome; NLRP, nucleotide-binding oligomerization domain receptors; NOD, nucleotide-binding oligomerization domain-containing protein; NSAID, nonsteroidal anti-inflammatory drug; SM, systemic mastocytosis; Th, T helper; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin.

sensitization and T-cell subsets may clearly distinguish between them (4).

Taken together, AD has increasingly been recognized as heterogeneous disease that should be respected in patient management, clinical research as well as drug studies (1, 2, 5).

New pathogenic insights

Atopic dermatitis, which usually precedes other atopic diseases, is thought to be reason for the atopic march (6) (Fig. 1). A defective epithelial barrier function, for example, due to filaggrin mutations (7), allows allergens as well as microbes and their products to enter the epithelium and initiate an inflammatory response. Otherwise, mediators produced by inflammatory cells may further impair skin barrier function. Histamine significantly suppressed the differentiation of epidermal keratinocytes by reducing the expression of tight junction proteins and desmosomal proteins, resulting in a thinning of the epidermis and stratum corneum (8). This effect could be abrogated by the H1 receptor antagonist cetirizine (8).

In AD lesions, an increased expression of interleukin (IL)-33, an epithelial-derived cytokine, and genetic polymorphisms of its receptors have been found (9). IL-33 has been reported to activate innate lymphoid cells (ILC), invariant natural killer T cells (iNKT), basophils and mast cells; stimulate dendritic cell maturation and migration and T helper 2 (Th2) differentiation; and enhance eosinophil survival (9). IL-33 has been shown to amplify IgE synthesis independent of the allergen via IL-4 produced by mast cells and eosinophils (10). Moreover, innate immune cells enhance antigen-specific immune responses as shown for ILC producing IL-4 and thus interacting with CD4⁺ T cell (11).

Thymic stromal lymphopoietin (TSLP) is another cytokine produced by epithelial cells, for example, upon injury, Toll-like receptor (TLR), or protease-activated receptor (PAR)-2 activation (12). It promotes Th2 inflammation, but also regulates Th17 responses (12–14). Skin-derived TSLP was found to enhance allergen sensitization and thus trigger allergic asthma by inducing IL-17 responses in the airways (14). Furthermore, TSLP may stimulate eosinophils to generate eosinophil extracellular traps (EETs) (15). Because of their ability to bind and kill bacteria, EETs are thought to be

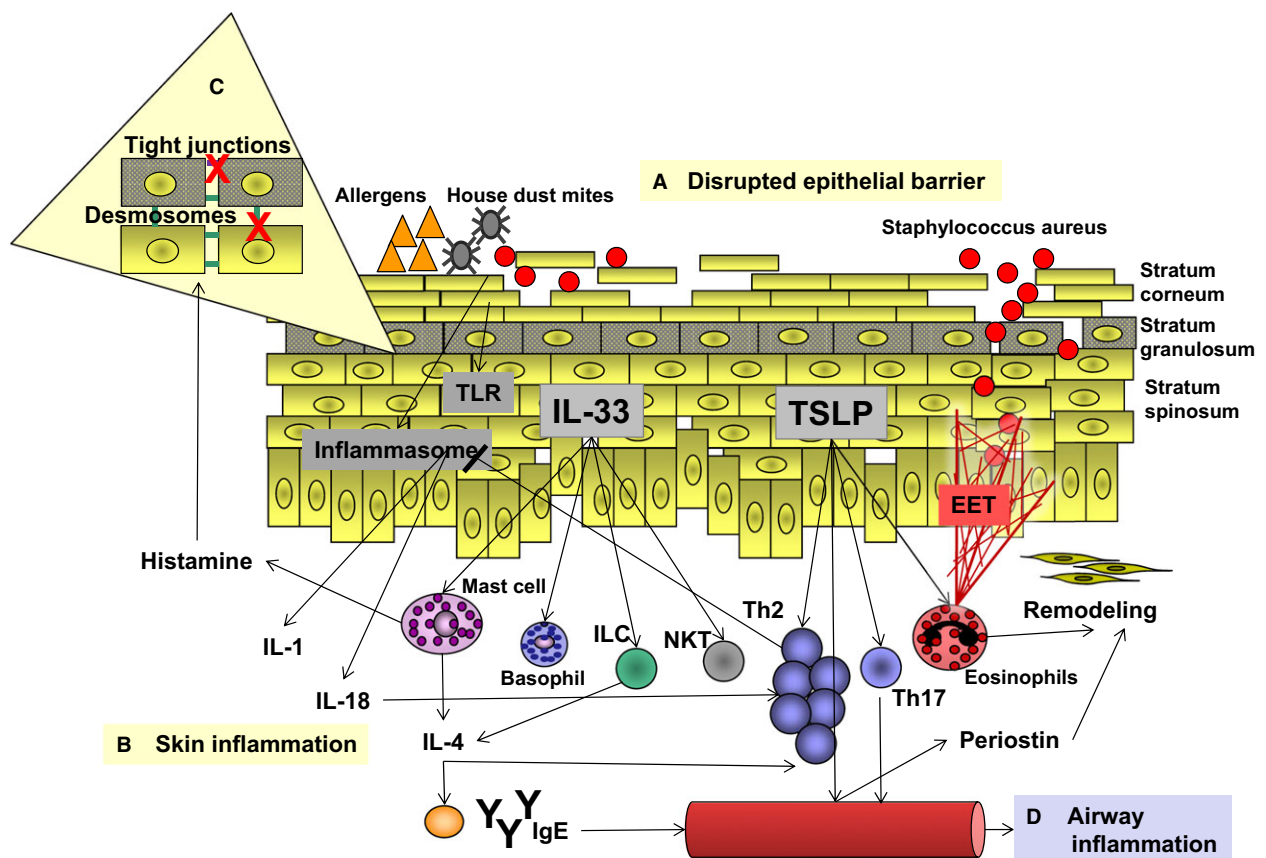


Figure 1 Novel insights into the pathogenesis of AD. (A) Because of a disrupted skin barrier, microbes and allergens might enter and activate keratinocytes to produce cytokines. (B) Thus, skin inflammation is initiated involving innate and adaptive immune cells. (C) Mediators released by inflammatory cells

further impair the skin barrier. (D) Cells and mediators derived from skin may spread and cause airway inflammation. EET, eosinophil extracellular trap; IL, interleukin; ILC, innate lymphoid cells; NKT, natural killer T cell; Th, T helper cell; TSLP, thymic stromal lymphopoietin.

produced as tools to fight against infectious agents penetrating a defective epithelial barrier (15, 16).

In addition to Th2 inflammation, IL-17 has been detected in early atopy-patch test reactions resembling acute AD (17). IL-17 and IL-22 expressions in the skin have been associated with remodeling in eczematous lesions (17). Periostin is yet another cytokine that has been linked to remodeling and tissue fibrosis (18). Periostin production by microvascular endothelial cells and fibroblasts has been shown to be refractory to corticosteroids (18).

Upon allergen-induced activation of the inflammasome, keratinocytes produced pro-inflammatory cytokines such as IL-1-beta and IL-18 that in turn might trigger Th2- and IgE-mediated immune responses (19). On the other hand, a downregulation of the inflammasome nucleotide-binding oligomerization domain receptor 3 (NLRP 3) in a Th2 cytokine milieu has been observed, which subsequently leads to an attenuated IL-1-beta response that might explain the increased susceptibility of patients with AD for infections with *Staphylococcus aureus* and herpes simplex virus (20). Products of *Staphylococcus aureus* were shown to modulate immune responses, for example, they downregulate FcεRI on Langerhans cells upon binding to TLR-2 (21). Upon TLR stimulation, dendritic cells enhance allergen uptake and depending on the ligand promote Th0 and/or Th1 responses (22).

Food-derived allergens have been suggested to lead to sensitization via the skin (23–25). When the house dust mite allergen Der p2 was applied on the skin, it induced a strong Th2 response independent of TLR4, and noteworthy, TLR4 expression rather protected against epicutaneous sensitization to Der p2 (26). In the presence of a TLR7 agonist, epicutaneous immunization to the birch pollen allergen Bet v1 induced a Th1 response and epicutaneous immunotherapy was able to suppress asthma in sensitized mice (27). There is increasing evidence that products used for skin care such as the antimicrobial substance triclosan increase the risk of sensitization to inhalant allergens (28).

Injection of IL-31, a cytokine known to link inflammation and itch, in the skin resulted in pruritus with a delayed onset, suggesting rather an indirect effect of IL-31 than a direct stimulation of cutaneous nerve fibers (29). Whereas the anti-pruritic effects of antihistamines are limited in patients with AD, a combined inhibition of histamine H1 and H4 receptors was shown to exert synergistic effects by inhibiting pruritus and inflammation in an animal model (30). Moreover, the stimulation of FcεRI on human monocytes promotes the differentiation of H1 receptor-expressing macrophages producing proinflammatory cytokines, assuming that H1 receptor blockers might have anti-inflammatory effects (31).

Several studies raised the question of gene–environment interaction (32, 33). Intense research is going on in order to identify children predisposed to develop AD. The protein spectrum of the vernix collected at birth might serve as biomarker to predict AD risk (34). In children with certain CD14 polymorphisms, early-life endotoxin exposure tended to exert a protective effect on atopy (35).

In summary, recent research data support the hypothesis that the atopic march starts in the skin. A defective barrier function and subsequent exposure of epidermal cells to microbes and allergens lead to an activation and interaction of innate and adaptive immune responses in the skin that may further promote allergic inflammation in the skin and airways.

Management of AD

Based on the progress in understanding the pathogenesis of AD and its role for the emergence of other allergic diseases, the concept of disease-modifying strategies for AD has been developed (36). Currently, a shift from avoidance strategies toward induction of tolerance and restoring skin barrier function has been recognized (37). So far, primary prevention with probiotics or neonatal vitamin A supplementation failed to significantly reduce allergic diseases including eczema (38–40). The effect of vitamin D on allergy is still under debate (41–44), but there is evidence that variances in vitamin D pathway genes modulate eczema risk and phenotypes in children (45).

In most patients with AD, topical therapy with emollients and/or anti-inflammatory agents is sufficient to control disease signs and symptoms, whereas systemic therapy should be considered for severe cases (46). As cyclosporine is the only substance that has been approved for systemic therapy of AD for a limited time in most European countries, off-label prescriptions might be required (47). Several biologics have been investigated showing positive effects in subgroups of patients with AD, for example, omalizumab (46, 48). Blocking of IL-4 and/or IL-13 and their receptors seems a very effective therapeutic approach for AD (49). In the past, clinical study designs and outcome measures have been very heterogeneous and thus difficult to compare. To standardize and adequately validate outcome measures in AD trials, the Harmonizing Outcome Measures for Eczema (HOME) initiative decided on four core outcome domains as well as identification and development of appropriate instruments (50).

Urticaria

Urticaria is a frequent mast cell-driven disease presenting with wheals and/or angioedema (51, 52) (Fig. 2). An epidemiological study revealed that chronic urticaria has mainly been associated with autoreactivity and alcohol consumption in a Chinese population (53). Interestingly, NSAID-induced urticaria does not evolve into chronic urticaria (54). Although chronic urticaria may spontaneously resolve, the improvement and remission rates are rather low, necessitating long-term management in a subgroup of patients (55). The recently published guidelines provide an actualized classification as well as diagnostic and therapeutic recommendations (51). Nonsedating H1 antihistamines are the first-line therapy for chronic urticaria and have been proven effective and safe in both spontaneous and inducible forms (56). To note, wheal and flare reactions can be induced independent of mast

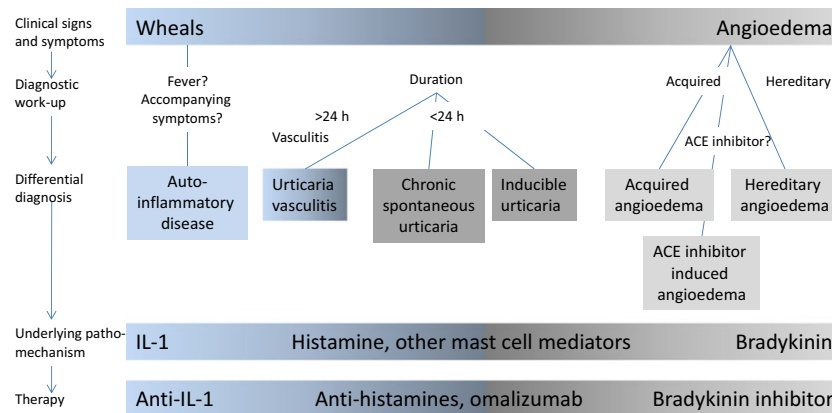


Figure 2 Diagnostic work-up of patients with wheals and angioedema, and therapeutic approaches based on pathomechanisms (modified from 66. 'Practical algorithm for diagnosing patients with recurrent

wheals or angioedema', Vol. 68, Iss. 6, 2013, 816–819. © 2013 John Wiley & Sons A/S. Published by John Wiley & Sons Ltd. This material is reproduced with permission of John Wiley & Sons, Inc.)

cell degranulation and histamine release, for example, by platelet-activating factor (PAF) (57). At this point, we want to emphasize that omalizumab, an anti-IgE antibody developed for asthma therapy (58–61), is effective in urticaria and currently listed as second-line therapy for chronic urticaria (51). In 2014, omalizumab has been approved for urticaria therapy in some European countries.

It became evident that autoimmune mechanisms play a causal role in a subgroup of patients with chronic spontaneous urticaria (62 Konstantinou). However, there is still a need to define clear diagnostic criteria and develop reliable diagnostic tests to identify these patients (62). In addition to autoimmune mechanisms, coagulation factors seem to participate in urticaria pathogenesis, and some patients with chronic spontaneous urticaria respond well to anticoagulant therapy (63). Moreover, psychosocial factors may contribute to the pathogenesis and exacerbation of chronic spontaneous urticaria (64).

Angioedema

Whether angioedema (AE) defined as localized and self-limiting edema of the subcutaneous and submucosal tissues due to a temporary increase in vascular permeability caused by the release of vasoactive mediators is associated with urticaria or not has an impact on diagnostic procedures and therapy (65, 66) (Fig. 2). AE has been classified to four types of acquired and three types of hereditary AE based on the pathogenesis, clinical and laboratory findings, and response to therapy (67). Because of unpredictable and potentially life-threatening attacks, AE significantly affects patients' quality of life (68). Treatment of AE comprises the acute intervention as well as prophylaxis of attacks (69). Icatibant, a bradykinin receptor antagonist, was shown to lead to a fast resolution of symptoms of hereditary and acquired AE and be effective for multiple attacks (70, 71). It has been proven suitable for self-administered therapy in patients with hereditary AE (72). Supplementation therapy with C1 esterase inhibitor (C1INH) is effective in treating acute attacks with

optimal effects when C1INH activity is restored to normal levels, as well as for prophylaxis (73, 74). Furthermore, ecallantide, an inhibitor of kallikrein, was reported to be effective for the therapy of acute hereditary AE attacks (75). As the risk of perioperative attacks in hereditary AE patients undergoing surgery has been estimated to be 6–30% (76), short-term prophylaxis with C1INH or danazol was applied, resulting in a significant reduction in postprocedural AE episodes (77).

Autoinflammatory diseases

Autoinflammatory diseases (AID) are a rare disease group characterized by IL-1-mediated innate immune reactions that often present with urticarial skin lesions and recurrent fever (78, 79) (Fig. 2). Both these papers provide a practical approach for diagnostic work-up and classification of AID to enable an effective treatment for patients with AID (78, 79). For instance, Schnitzler's syndrome is characterized by recurrent urticarial rash and monoclonal gammopathy associated with signs of inflammation such as recurrent fever, objective signs of abnormal bone remodeling, elevated CRP level or leukocytosis, and a neutrophilic infiltrate on skin biopsy (80). Blocking IL-1, for example, with anakinra, canakinumab, and also rilonacept, has been reported to result in a rapid clinical response (80, 81).

Mastocytosis

As mastocytosis in the skin is an important indicator for systemic mastocytosis (SM), a systematic work-up including bone marrow biopsy for adult patients is recommended because of therapeutic and prognostic implications (82). The KIT D816V is present in most patients with SM, and the KIT D816V allele burden has been identified as a prognostic factor for survival that significantly correlates with SM subgroups (cutaneous mastocytosis < indolent SM < smoldering SM < aggressive SM) and SM with associated hematologic nonmast cell lineage disease as well as

tryptase levels (83). For the diagnosis of SM that manifests without urticaria pigmentosa lesions and often has a low mast cell burden, highly sensitive diagnostic methods including multiparameter flow cytometry immunophenotyping for the identification of BMCMC and the KIT mutation analysis of highly purified BMCMC have successfully been applied (84). Recently, the mast cell activation syndrome (MCAS) has been recognized as novel entity. To establish the diagnosis of MCAS, the following criteria should be fulfilled: 1) clinical signs of severe recurrent (or chronic) systemic mast cell activation are present, 2) involvement of mast cells can be documented by biochemical measurements (e.g., increase in tryptase), and 3) the symptoms respond to therapy with mast cell-stabilizing agents or drugs directed against mast cell mediator production, mediator release, or mediator effects (85).

IgG4-related disease

IgG4-related disease (RD) is another newly recognized entity characterized by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations (86). Although many patients present with blood eosinophilia and elevated total IgE levels assuming an allergic mechanisms, most of the patients with IgG4-RD are nonatopics, suggesting that the disease itself contributes to eosinophilia and IgE elevation (86).

Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a common eczematous skin disease that may come together with AD. Skin barrier abnormalities, an altered bacterial colonization, an increased topical allergen exposure, and the disturbed Th1/Th2 balance have been identified as factors affecting the association between ACD and AD (87). However, the exact interactions and the effects of contact sensitizations on IgE-mediated allergy remain to be investigated (87). Upon stimulation with nickel and palladium, an increased proliferation of IL-5 and IL-13 and cytokine production by T cells isolated from peripheral blood have been reported that correlated with positive skin test reactions, suggesting that Th2 in addition to Th1 cytokines play a role in the elicitation of contact allergy (88). Although corticosteroids are used as first-line therapy for allergic diseases, they themselves can induce ACD in sensitized patients, of which 5% develop generalized eczematous or maculopapular eruptions due to systemic contact dermatitis after oral or parental reexposure mainly to group I molecules such as methylprednisolone (89).

Drug hypersensitivity

Adverse drug reactions (ADRs) are one of the major causes of iatrogenic disease, and cutaneous ADRs (cADRs) are the most common form (90). Yet, the diagnosis, management, and pathogenesis of cADRs remain a challenge to clinicians

and a field of intensive study in research. In the recent years, several advances have been made.

The latest position papers

Common and systematic approaches for the diagnosis, classification, and management of drug hypersensitivity reactions are undoubtedly needed to improve outcomes and research. Still, there are only few standardized guidelines and consensus documents to guide medical decision making related to drug hypersensitivity. In this respect, considerable efforts have been made in recent years and important consensus and position papers have been published. Most prominently, an international consensus on drug allergy was formulated, highlighting key similarities between existing guidelines and identifying their deficiencies. This international consensus provides a comprehensive reference document for the diagnosis and management of drug hypersensitivity reactions (91).

More specific position papers have also been formulated. The EAACI Task Force on nonsteroidal anti-inflammatory drugs (NSAIDs) hypersensitivity proposes uniform definitions, algorithms, and classifications of hypersensitivity reactions to NSAIDs and provides recommendations for the management of hypersensitive patients (92, 93). Following the proposed algorithms, Yilmaz et al. (94) analyzed hypersensitivity to NSAIDs in children and found that diagnostic tests are necessary in children to predict and/or diagnose hypersensitivity to NSAIDs, although a family history of NSAID hypersensitivity showed significant predictive value.

A further position paper reviews the literature, presents the expert opinion of the Drug Hypersensitivity Interest Group of the EAACI on desensitization in delayed drug hypersensitivity reactions, and concludes that slower protocols appear to be more effective than rush protocols (95).

Epidemiology and genetics of drug hypersensitivity

The prevalence of immediate reactions to beta-lactams shows considerable heterogeneity worldwide, suggesting a genetic influence. Accordingly, links between genetic determinants of atopy and immediate-type allergy to beta-lactams have been suggested (96). In two studies, the relation between allergy to beta-lactams and gene polymorphisms and determinants of atopy, respectively, have been analyzed (96, 97). Whereas the influence of nucleotide-binding oligomerization domain-containing protein 2 (NOD2) polymorphisms seems to be population dependent (97), polymorphisms in the interleukin-4 receptor might contribute to the high prevalence of beta-lactam allergy in the south of Spain. Furthermore, determinants of atopy such as total IgE and specific IgE against prevalent allergens were also linked to immediate-type allergy to beta-lactams (96). These preliminary results merit further investigation and hold promise for future risk assessment strategies.

In recent years, it became clear that certain human leukocyte antigen (HLA) alleles are strongly associated with hypersensitivity to particular drugs (98, 99). As drug-activated T cells are key mediators of drug hypersensitivity and HLA molecules are crucial in T-cell stimulation, the discovery of

the involvement of particular HLA alleles in drug hypersensitivity constitutes a significant step forward in our understanding of drug hypersensitivity (100). However, additional but yet unknown factors are also involved in determining whether an individual can tolerate a drug: In some cases such as carbamazepine hypersensitivity in HLA-B*15:02-positive patients, the presence of the specific HLA allele is not sufficient for disease development but also a certain T-cell receptor (TCR) repertoire is required (101). In allopurinol hypersensitivity, the presence of HLA-B*58:01 allele substantially increases the risk of allopurinol hypersensitivity, but it is not an absolute requirement (102). Therefore, further studies elucidating the complex interactions between drugs, HLA molecules, and T-cell receptors are needed to better understand and predict drug hypersensitivity (100).

Pathophysiology/Disease mechanisms

Sequential reactivations of several herpes viruses have been demonstrated in severe cADRs, most notably in the acute stage of drug rash with eosinophilia and systemic symptoms (DRESS) (Fig. 3). A study investigating viral reactivation long term has found that distinct patterns of herpes virus reactivation can be linked to clinical phenotypes of severe cutaneous adverse drug reactions (SCARs) and that they might be affected by the use of systemic corticosteroids (103). During flaring of symptoms in DRESS patients, monomyeloid precursors emerge in the circulation expressing HHV-6 antigen. It has now been proposed that these cells are attracted to the skin via HMGB-1 where they promote HHV-6 transmission to skin-infiltrating CD4⁺ T cells, thus

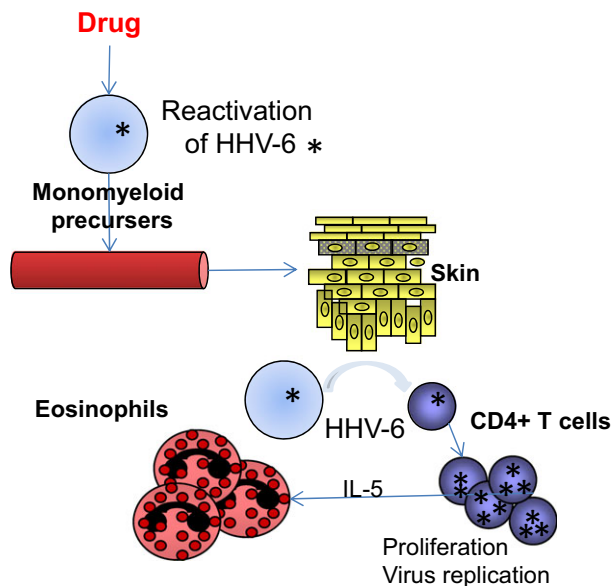


Figure 3 Herpes virus reactivation in drug rash with eosinophilia and systemic symptoms (DRESS). In DRESS, monomyeloid precursor cells expressing HHV-6 antigen transfer the antigen to CD4⁺ T cells in the skin, resulting in virus replication and T-cell proliferation and subsequent eosinophilia.

enabling HHV-6 replication. Together, these findings raise the possibility that the skin is the primary site of initial HHV-6 reactivation in DRESS (104).

One of ten patients with drug hypersensitivity develops multiple drug hypersensitivities (MDH), a phenomenon that is incompletely understood. Suspecting a dysfunction of immune regulation, Daubner et al. investigated regulatory T cells in MDH patients but found no functional deficiencies in these cells. However, they discovered that the drug-reactive T cells are contained in a population of preactivated T cells that may therefore show a lower threshold for activation by drugs (105). Drug-specific T cells are known to play a central role in cADRs. A study by Nihm et al. (106) found that roughly three of 10 million T cells in the circulation of healthy donors are specific to benzylpenicillin, thus proving the existence of naïve CD4⁺ T cells specific to this compound.

Idursulfase is used for enzyme replacement therapy in Hunter syndrome (mucopolysaccharidosis type II), but various forms of drug hypersensitivity reactions limit its use. It has now been shown that anaphylaxis after infusion of idursulfase is mediated by anti-idursulfase IgE antibodies, which can be detected by skin prick testing (107).

Diagnostics in drug hypersensitivity

Diagnosis of penicillin allergy

In an intriguing study, Hjortlund et al. (108) studied the validity of the guidelines for the diagnosis of allergy to β -lactam antibiotics proposed by the European Network for Drug Allergy (ENDA). The authors show that distinction between immediate reactors and nonimmediate reactors based on case history is often insufficient and that a 7-day challenge with the culprit β -lactam may be more appropriate than the accepted 2-day challenge and that skin testing may yield unreliable results (108).

In patients with hypersensitivity to penicillins in need of appropriate alternative antibiotic treatment, the use of carbapenems has been hampered by suspected cross-reactivity between penicillins and both imipenem and meropenem. In a study of subjects with T-cell-mediated hypersensitivity to penicillins, the absence of clinically significant T-cell-mediated cross-reactivity between penicillins and carbapenems has now been demonstrated, thus giving clinicians an important antibiotic alternative (109). However, pretreatment skin tests and graded challenges are still advised in subjects who experienced severe reactions (109).

Skin testing in drug hypersensitivity

For the evaluation of drug hypersensitivity reactions, skin tests are indispensable. However, there is a lack of standardized protocols, often preventing a thorough work-up of suspected drug hypersensitivity. To promote and standardize reproducible skin testing in the clinical practice, the EAACI Interest Group on Drug Allergy has published a position paper, in which specific drug concentrations for beta-lactam antibiotics, perioperative drugs, heparins, platinum salts, and radiocontrast media are defined (110). A prominent example

for this allergological challenge is testing of suspected allergies to the clinically important antibiotics such as ciprofloxacin, clarithromycin, and rifampicin. Broz et al. (111) show that using a practical algorithm, standardized skin testing protocols for these broadly used non-beta-lactam antibiotics can be defined, making them applicable for clinical practice.

In patients with hypersensitivity reactions to anesthetics and pending surgery, there can be a need for immediate allergological assessment. In a prospective study of patients with allergic reactions during anesthesia, skin testing as early as 4 days after the initial reaction is useful and could minimize false-negative results, but should be viewed as a complement to later skin testing (112).

Intralesional pentavalent antimonials are considered the first-line treatment of cutaneous leishmaniasis. However, local reactions at the injection sites can complicate therapy. In a series of patients with local injection reactions, evidence for type IV hypersensitivity to meglumine antimoniate was now described for the first time (113).

It has been reported that skin test sensitivity to penicillins can decrease over time and that allergic patients may lose sensitivity if the responsible compounds are avoided. This phenomenon was now also observed for patients with IgE-mediated hypersensitivity to cephalosporins (114). On the other hand, predicting immediate hypersensitivity to cephalosporin before its administration using intradermal skin testing was found to be obsolete, because of the very low sensitivity and predictive value of the test (115).

Nonimmediate hypersensitivity reactions to iodinated contrast media are frequent and remain a diagnostic challenge. In a placebo-controlled study, skin testing has been found to be insufficient as a diagnostic tool. Drug provocation tests are thus necessary to confirm diagnosis (116).

In the case of immediate hypersensitivity reactions to radiocontrast media, it was shown that basophil activation tests might be an alternative to skin testing and provocation tests, although the diagnostic value remains to be investigated further (117, 118).

Meat allergy? Test a cancer drug!

There are rare reports of severe hypersensitivity reactions to red meat in patients with IgE to alpha-gal (galactose-alpha-1,3-galactose). In an elegant study, Michel et al. (119) found that skin prick tests and basophil activation test using cetuximab, a monoclonal antibody carrying the alpha-gal epitope, may be a more sensitive alternative in patients with an assumed allergy to meat.

Desensitization to vitally important anticancer drugs

Because of their vital indication for many patients with tumor, desensitization to antineoplastic agents has become an important strategy if drug hypersensitivity has developed. In a prospective study, a new desensitization program has shown to be an effective therapeutic tool for hypersensitivity to several antineoplastic agents (120).

Need of work-up of drug-mediated anaphylaxis by allergists

Anaphylaxis is defined as a life-threatening reaction resulting from mast cell-derived mediator release, with one of the main causes of anaphylactic shock being drugs (121). However, cases of drug anaphylaxis are rarely documented by allergy tests, leading to a lack of solid data, which is needed to prevent further reactions. In an analysis of over 300 cases, Renaudin et al. (122) support the need for a work-up of anaphylaxis patients by trained allergists based on a common methodology of diagnosis. They propose a three-step procedure for allergy assessment including firstly skin tests, secondly *in vitro* tests, and finally oral challenge.

The skin will stay in focus

This update has clearly demonstrated how broad the spectrum of research and clinical activities in the field of allergic skin diseases has been. *Allergy* provided valuable guidelines and practical advices, for example, where to prick the apple to identify sensitized patients (123), the employment of medical clowns to overcome anxiety and pain in children undergoing skin prick test (124), and touched ethical problems such as the significance and relevance of allergen expression tests of genetically modified plants in order to evaluate their potential risk to induce allergy, because reliable tests are not available so far (125). Understanding the role of the skin in the emergence of allergic diseases will help to develop novel preventive, diagnostic, and therapeutic strategies and thus improve patient management in both primary care (126) and specialized medicine providing individualized treatment (5). An effective disease management including prevention and disease-modifying strategies would allow to significantly decrease the burden on patients and society as allergic diseases cause an immense socioeconomic burden (1, 127).

Conflicts of interest

The authors declare that they have no conflicts of interest.

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