

REVIEW ARTICLE

Atopic dermatitis and skin allergies – update and outlook

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To cite this article: Wollenberg A, Feichtner K. Atopic dermatitis and skin allergies – update and outlook. *Allergy* 2013; **68**: 1509–1519.

Keywords

atopic dermatitis; chronic urticaria;
drug allergy.

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Accepted for publication 12 October 2013

DOI:10.1111/all.12324

Edited by: Thomas Bieber

Abstract

During the last few years, an impressive amount of experimental studies and clinical trials have dealt with a variety of distinct topics in allergic skin diseases – especially atopic dermatitis. In this update, we discuss selected recent data that provide relevant insights into clinical and pathophysiological aspects of allergic skin diseases or discuss promising targets and strategies for the future treatment of skin allergy. This includes aspects of barrier malfunction and inflammation as well as the interaction of the cutaneous immune system with the skin microbiome and diagnostic procedures for working up atopic dermatitis patients. Additionally, contact dermatitis, urticaria, and drug reactions are addressed in this review. This update summarizes novel evidence, highlighting current areas of uncertainties and debates that will stimulate scientific discussions and research activities in the field of atopic dermatitis and skin allergies in the future.

A variety of distinct topics in allergic skin diseases and especially atopic dermatitis (AD) has been addressed in the biomedical literature published during the last few years. Recent work has focused on many clinical and pathophysiological aspects of allergic skin diseases, discussing promising targets and strategies for the future treatment of skin allergies (1, 2). In this review, we summarize novel evidence and highlight current areas of research in AD, contact dermatitis, urticaria, drug reactions, and other allergic skin diseases.

Abbreviations

AD, atopic dermatitis; CU, chronic spontaneous urticaria; DOCK8, dedicator of cytokinesis 8 protein; DRESS, drug rash with eosinophilia and systemic symptoms; EASI, Eczema Area and Severity Index; EH, Eczema herpeticum; FcεRI, high-affinity IgE receptor; HIES, Hyper-IgE syndromes; HR, histamine receptor; HHV, human herpesvirus; HSV, herpes simplex virus; IgE, immunoglobulin E; IL, interleukin; LGG, *Lactobacillus rhamnosus* GG; MC, Mast cells; MCID, minimal clinically important difference; PPAR, Peroxisome proliferator-activated receptor; POEM, Patient-Oriented Eczema Measure; PO-SCORAD, Patient-Oriented SCORing of Atopic Dermatitis; SCORAD, SCORing of Atopic Dermatitis; STAT3, signal transducer and activator of transcription 3.

Risk factors and severity scoring of atopic dermatitis

AD is a common, clinically defined skin disease frequently associated with allergic rhinitis, asthma, and immunoglobulin E (IgE)-mediated food reactions (3, 4). The high variability of clinical phenotype and severity, genetic background, and known pathomechanisms strongly suggests a high degree of pathophysiological heterogeneity (5). Although the clinical pattern of eczematous skin lesion is relatively uniform, AD often shows distinct progression patterns, hence requiring personalized prevention and management strategies (5).

Determinants of AD were extracted from the public-use files of the German Interview and Examination Survey for Children and Adolescents (KIGGS) study, a nationwide cross-sectional representative survey including 17 641 German children aged 0–17 years with a response rate of 66.6% (6). The weighted prevalence of ever physician-diagnosed eczema was 13.2% (95% CI 12.5–13.9%), with significant positive associations between parental allergies (OR 1.94, 95% CI 1.72–2.19), parent-reported infection after birth (OR 1.45, 95% CI 1.05–2.00), and parent-reported jaundice after birth (OR 1.27, 95% CI 1.04–1.54). Being a migrant (OR 0.63, 95% CI 0.49–0.80) and keeping a dog (OR 0.78, 95% CI 0.64–0.96) showed significant inverse associations with eczema. Other lifestyle (alcohol consumption during pregnancy) and environmental factors (mold on the walls, pets)

were not significantly related to AD (6). Therefore, early life factors such as perinatal health problems may also be important for AD manifestation (6).

A recent systematic review points out that patients with current parasite infection (*Ascaris lumbricoides* or other worms) have a decreased risk of allergen sensitization (OR 0.69; 95% CI 0.60–0.79; $P < 0.01$) (7). Therefore, intestinal parasite infection appears to protect against allergic sensitization. On the other hand, a randomized vitamin A supplementation in early life showed an increased risk of atopy in a clinical trial including 281 children (8).

An epidemiological study addressed the development of eczema, asthma, and rhinitis in relation to sex and parental allergy from a data set of 2916 children, 58% of whom had had eczema, asthma, and/or rhinitis before their 12th year of life (9). Parental allergy was associated with increased comorbidity, more persistent disease, and an increased risk of having any allergy-related disease up to 12 years (OR 1.76; 95% CI 1.57–1.97). Boys had an increased risk of allergic disease throughout childhood (9).

A prenatal, randomized, unblinded, controlled study aimed at AD prevention examined potential preventive effects of prenatal *Lactobacillus rhamnosus* GG (LGG). 250 pregnant women carrying infants at high risk of allergic disease received probiotic supplementation (LGG 1.8×10^{10} cfu/day) from 36 weeks after gestation until delivery (10). Prenatal probiotic treatment did not reduce the risk of intrinsic (34% probiotic, 39% placebo; RR 0.88; 95% CI 0.63, 1.22) or extrinsic AD (18% probiotic, 19% placebo; RR 0.94; 95% CI 0.53, 1.68), demonstrating that prenatal LGG is insufficient for preventing eczema (10).

Although a high proportion of AD patients undergo remission during childhood, severe cases may persist until adulthood. New retrospective data support a clinical classification into five main course types (11). The strongest differences in the sensitization pattern and predilection site of skin lesions were observed between those patients with an early type of onset of AD showing a chronic persisting course until adulthood and those patients with a later onset of AD after the 20th year of life (11).

Severity scoring of AD targets either exclusively objective signs or subjective symptoms or a combination of both. SCORing of Atopic Dermatitis (SCORAD) and Eczema Area and Severity Index (EASI) are the most widely used scoring systems, with the objective SCORAD being defined as the objective data part of the composite SCORAD score (12).

SCORAD, the objective SCORAD, EASI, and the Patient-Oriented Eczema Measure (POEM) have been assessed in a study investigating the responsiveness (synonymous with sensitivity to change) and minimal clinically important difference (MCID) of these scores (13). Using trial data from three randomized controlled trials, the objective SCORAD and SCORAD showed a fair responsiveness, and the MCID was 8.7 points for the SCORAD, 8.2 for the objective SCORAD, 6.6 for the EASI, and 3.4 for the POEM (13).

As patient-oriented medicine is an emerging and WHO-encouraged concept, a Patient-Oriented SCORing of Atopic Dermatitis (PO-SCORAD) index has been developed and

validated for self-assessment of AD severity by the patient (14). The validation of the PO-SCORAD was achieved in a large group of 471 European AD patients exhibiting all forms of AD severity by assessing its correlation with the SCORAD index (14). PO-SCORAD and SCORAD scores at day 0 were significantly correlated ($r = 0.67$, $P < 0.0001$), and the consistency was confirmed at day 28 ($r = 0.79$, $P < 0.0001$), with the SCORAD showing a higher responsiveness than the PO-SCORAD (14).

The Harmonising Outcome Measures for Eczema (HOME) initiative, an international multiprofessional group dedicated to AD outcomes research, conducted a consensus meeting in Amsterdam in June 2011 to determine core outcome domains for AD trials and define quality criteria for outcome measures (15). Consensus was achieved to include clinical signs, symptoms, long-term control of flares, and quality of life into the core set of AD trial outcome domains to be reported as primary or secondary endpoints in future AD trials. Measures of these core outcome domains need to be valid, sensitive to change, and feasible (15).

Barrier function in atopic dermatitis

Recent reviews facilitate an understanding of the complex physiology of epidermal barrier formation. This knowledge is essential for a critical assessment of the various emollient products available for AD (16, 17).

A novel function of the histamine 1 receptor (HR1) in AD was identified using a human skin model of epidermal differentiation: Histamine reduced the differentiation capacity of cultured keratinocytes and the expression of the tight junction proteins zona occludens-1, occludin, claudin-1, and claudin-4. The Desmosomal junction proteins corneodesmosin and desmoglein-1 were also downregulated by histamine (18). These findings suggest that mast cell (MC) activation and histamine release may contribute to skin barrier defects in AD.

Alterations in genes affiliated to epidermal barrier function, such as the profilaggrin gene, are risk factors for AD and AD patients' susceptibility to bacterial and viral skin infections. Quite a number of genetic studies of the profilaggrin gene have confirmed an association of this gene responsible for ichthyosis vulgaris with clinical AD manifestations – an association clinically well known since decades. These include reports of cohorts and study groups from many countries including Ireland (19), Germany (20), Denmark (21), and China (22). As Th2 cytokines from the T-cell infiltrate in AD lesions downregulate filaggrin production on the protein level (23), filaggrin protein deficiency contributes to AD development also in AD patients without filaggrin mutations.

Filaggrin is the main source of several major components of natural moisturizing factor (NMF) in the stratum corneum including pyrrolidone carboxylic acid (PCA) and urocanic acid (UCA). A reduced level of PCA, UCA, and histidine in patients with FLG deficiency or non-filaggrin-mutated AD (24) may be regarded an expected finding. Multiple regression analysis confirmed that NMF levels were

independently associated with FLG genotype and severity of AD (24). However, defects in tight junction formation contribute also to the barrier defects in AD (25).

Innate and adaptive immunity in atopic dermatitis

AD can be seen as a combination of an impaired innate and a distorted adaptive immunity interacting together in the framework of a cutaneous immune system with suboptimal barrier function (26). A tendency toward Th2-dominated immune responses and predominance of the associated Th2 cytokines interleukin (IL)-4, IL-5, and IL-13 is by tradition the most cited explanation for allergic diseases (27). Novel insights into immunobiological research have broadened this view considerably (28). Facilitated antigen presentation mediated by IgE bound to the high-affinity IgE receptor (FcεRI) on epidermal dendritic cells (29, 30) is an important aspect of the pathogenesis (Fig. 1) of at least extrinsic AD (31). A global as well as FcεRIγ-chain-specific hypomethylation of DNA of AD patients may contribute to the overexpression of FcεRI on monocytes isolated from AD patients (32).

The existence of AD in the absence of detectable IgE against common aeroallergens and food allergens has interested dermatologists and allergists since the discovery of IgE (33) and may be explained by viewing AD as a primarily cell-mediated, delayed-type hypersensitivity disease with an

optional component of IgE-mediated sensitization (26). Although the phenotype of extrinsic and intrinsic AD may be similar, extrinsic patients express higher levels of FcεRI on their cell surface (34). In addition, clinically severe AD patients are 'more atopic' than mild AD patients (35). Thereby, the switch from intrinsic to extrinsic AD seems to occur early in life (36).

Vitamin D plays a key role in innate and adaptive immunity by stimulation of Toll-like receptors, increasing pro-inflammatory cytokine production, and possibly enhancing T-helper type 2 responses (37). The data relating vitamin D to allergic skin diseases have recently been reviewed (37) and are equivocal with studies linking both high and low vitamin D levels to an increased risk of developing AD. Vitamin D is an essential factor for the generation of the antimicrobial peptide LL37 in keratinocytes, the only human cathelicidin known so far. A recent study confirmed that serum levels of LL-37 and 25-hydroxyvitamin D3 were decreased in patients with AD compared with normal donors and were correlated in both groups (38).

Moreover, synthetic vitamin D receptor agonists mediating immunomodulatory activities without the adverse hypercalcemic effects of the natural receptor ligand calcitriol suppress IgE production by human peripheral B cells, an effect possibly mediated by reduced activation-induced deaminase (AID) and IgE-secreting cells (39).

One of the main functions of IL-31, a cytokine produced by T cells, is pruritus induction in AD skin (40). Effects are transmitted through a heterodimeric receptor composed of IL-31RA and OSMR expressed on epithelial cells including keratinocytes. STAT-3 phosphorylation is activated by IL-31 in human keratinocytes and augmented after pre-activation with Pam3Cys or IFN-γ (41). IL-31 enhances the secretion of CCL2 after upregulation of the receptor with Pam3Cys or IFN-γ in a TLR-2-dependent mechanism (41). This new link between TLR-2 ligands and IL-31 may be important for AD lesions colonized by *S. aureus* (41).

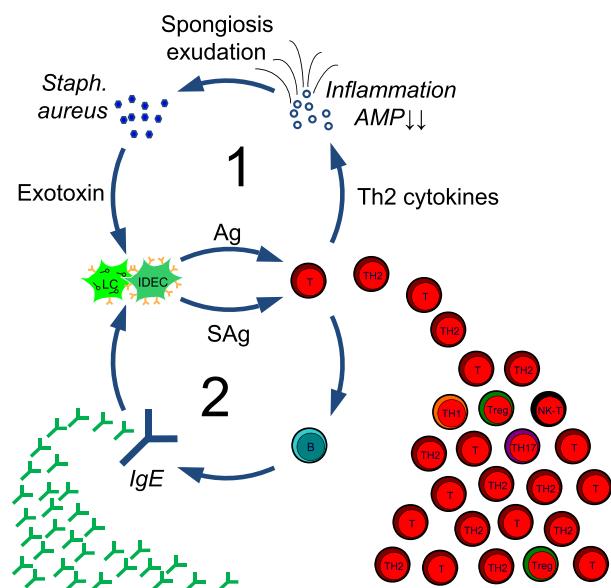


Figure 1 The vicious circles of atopic dermatitis. A powerful, superantigen-driven vicious circle involving downregulation of antimicrobial peptides, staphylococcal overgrowth, and production of immunoactivating toxins with superantigenic properties interacts with an antigen-specific vicious circle involving IgE production and binding to high-affinity IgE receptors expressed on skin dendritic cells followed by IgE-mediated, facilitated antigen presentation. Innate immunity and adaptive immunity are dysfunctional in atopic dermatitis lesions and may cause severe disease flares.

Colonization and infection in atopic dermatitis

AD patients are susceptible to *S. aureus* skin infections. These staphylococci may produce several exotoxins with superantigenic properties, and patients sensitized to SEB show more severe AD lesions (42). Toll-like receptors (TLRs), especially TLR-2, recognize cell wall components of *S. aureus*, for example, lipoteichoic acid and peptidoglycan (43). Monocytes of patients with a heterozygous TLR-2 polymorphism TLR-2 R753Q, which is associated with clinically severe AD, produce significantly more IL-6 and IL-12 upon TLR-2 activation compared with nonmutated AD patients. The overgrowth of staphylococci during AD flares is clearly associated and possibly preceded by a loss of diversity in the skin microbiome of AD patients (44). AD patients have a disbalanced innate and acquired immunity connected to staphylococci (43).

S. aureus produces extracellular, protein containing vesicles in culture, which may be isolated by ultracentrifugation of the culture media (45). The *in vitro* application of these

vesicles increased the production of various pro-inflammatory mediators like IL-6, thymic stromal lymphopoietin, macrophage inflammatory protein-1 α , and eotaxin by dermal fibroblasts. These vesicles caused epidermal thickening if applied to tape-stripped skin, with infiltration of the dermis by MC and eosinophils, and increased cutaneous production of IL-4, IL-5, IFN- γ , and IL-17. Contact with *S. aureus*-derived extracellular vesicles appears sufficient to induce AD-like skin inflammation (45).

Eczema herpeticum (EH) is defined as the disseminated infection of an eczematous skin disease with the herpes simplex virus (HSV) – in clinical reality almost exclusively in AD (46). Unmasking of the HSV entry receptor nectin-1 in adherence junctions (47), a lack of plasmacytoid dendritic cells in AD lesions (48), a deficiency of cathelicidin production *in situ* (49), and an abnormal interferon- γ response to HSV (50) contribute to EH pathogenesis. Clinical risk factors for EH are known from a study involving 100 EH cases and 105 controls, and include an early onset and high clinical severity of the underlying AD and high total serum IgE levels (51). Lymphopenia and fever are hallmarks of acute EH episodes (51).

A recent study of 235 adult subjects with or without a history of AD, EH, or HSV infection including 52 EH cases was analyzed for EH risk factors (52). The results showed more male than female EH patients, lymphopenia, and monocytoysis during acute EH episodes. AD patients with recurrent HSV infection and a history of EH showed higher total serum IgE levels, more severe AD, and higher IgE sensitization profiles than those without an EH history (52).

Diagnostic procedures and differential diagnosis of atopic dermatitis

As AD is a clinically defined disease entity, the diagnosis is based on clinical features. Contact dermatitis and perioral dermatitis are among the differential diagnoses of localized cases. Hyper-IgE syndromes (HIES) may be a challenging differential diagnosis for severe AD. Diagnostic procedures are mostly performed to characterize either the IgE-based sensitization spectrum or delayed-type hypersensitivity reactions of concomitant contact allergy. Microbiological tests identifying bacteria and viruses can be helpful to diagnose or exclude infections as differential diagnoses (53). The skin prick test is optimal for screening the immediate-type sensitization spectrum against aeroallergens and food allergens, and well-performed prick-to-prick tests may be useful for rare allergens (54).

The atopy patch test (APT) is a patch test procedure for delayed-type hypersensitivity reactions against protein allergens known to elicit IgE-mediated type I sensitization in atopic patients and may reveal type IV sensitization in patients who are negative for the respective type I tests (55). The APT uses intact protein allergens instead of haptens in an optimized test setting and with a special reading key (56). It may be clinically useful especially for AD, as the currently available tests either target the wrong reaction type (type I instead of type IV) or use the wrong allergens (haptens

instead of protein allergen) (55). Positive APT reactions correlate with lymphocyte transformation test results and allergen-specific Th2 cells in the peripheral blood (57). The ETFAD has developed a standardized APT technique: Intact protein allergens, purified in petrolatum, are applied in 12-mm diameter Finn chambers mounted on Scanpor tape for 48 h to nonirritated, nonabraded, or tape-stripped skin of the upper back for 48 h (58). The evaluation of test reactions is performed after 48 and 72 h using the ETFAD reading key assessing erythema, number, and distribution of papules (58). A recent APT trial aimed to investigate the benefit of APTs in predicting oral tolerance in 172 children with non-IgE-mediated cow's milk allergy and gastrointestinal symptoms (59). The prospective study evaluated 172 subjects with confirmed non-IgE-mediated cow's milk allergy, 113 of which had positive APTs to cow's milk proteins. An APT was performed again after 12 months of exclusion diet. The APT results correlated significantly ($P < 0.001$) with the oral food challenge (sensitivity 68%; specificity 88%) (59). The authors see a value of the APT by contributing to determine whether an oral food challenge can safely be undertaken (59).

The HIES are clinically important differential diagnoses of severe AD and show eczematous skin disease, increased serum IgE, and recurrent infections. The autosomal dominant HIES form is caused by heterozygous mutations in the signal transducer and activator of transcription 3 gene (STAT3-HIES) and is associated with skin and internal abscesses, recurrent pneumonia, pneumatoceles, connective tissue and skeletal abnormalities, and mucocutaneous candidiasis. The autosomal recessive form results from loss-of-function mutations of the dedicator of cytokinesis 8 protein gene (DOCK8-HIES) and is associated with eczematous skin disease and recurrent viral infections. Although AD and both subtypes of HIES show significantly increased IgE levels, recent data indicate that AD patients are predominantly sensitized against aeroallergens, whereas DOCK8-HIES patients are mounting their IgE responses mostly against food allergens, and the specificity of the IgE in STAT3-HIES remains largely unknown (60). This corresponds nicely to the frequently observed clinical phenotype of DOCK8-HIES patients with concomitant food allergy and relative absence of clinical allergy in STAT3-HIES patients (61). Dermatologists and allergists should be aware of HIES as a possible differential diagnosis in their AD patients and be trained to evaluate them for HIES in suggestive patients (60). In clinical reality, a stepwise approach regarding the diagnostic procedures is recommended (60).

Therapeutic options for atopic dermatitis

A wide variety of treatment modalities has been described for AD. A combination of emollient therapy, anti-inflammatory therapy, and antimicrobial therapy is regarded optimal for most patients (62, 63). Disease-modifying strategies such as subcutaneous immunotherapy (64) or targeted therapy with biologics are just emerging. The current position paper of the European Task Force on Atopic Dermatitis (ETFAD), which is also the EADV Eczema Task Force (53), and the

current EDF guideline on AD management provide excellent sources of information for the clinician (65, 66).

The traditional topical anti-inflammatory treatment is the reactive application of topical anti-inflammatory agents such as topical corticosteroids (TCS) and topical calcineurin inhibitors (TCIs). These differ in mode of action, as well as effects on skin barrier function (67) and on the inflammatory cell infiltrate (68, 69). The short-term benefit of this approach is well established, but long-term remission between flares is difficult to achieve. Normal looking, nonlesional skin of AD patients is immunobiologically not normal, but harbors invisible inflammation and a barrier defect (70). This has led to the novel concept of proactive therapy, which is defined as long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin (71). A number of larger clinical trials with the TCS fluticasone propionate and methylprednisolone aceponate and with the TCI tacrolimus have followed this approach (72).

Recent work has confirmed the different modes of action of TCS and TCI in AD by gene expression profile analysis, which was performed on lesional AD skin samples after topical treatment with the TCS betamethasone valerate or the TCI pimecrolimus (67). Betamethasone valerate reduced the mRNA levels of various genes encoding markers of immune cells and inflammation, dendritic cells, T cells, cytokines, chemokines, and serine proteases. Pimecrolimus exerted minor effects only (67), thus mirroring the higher clinical efficacy of betamethasone valerate compared with pimecrolimus. The reduced expression of filaggrin and loricrin in AD lesions was normalized by both drugs. Betamethasone valerate, but not pimecrolimus, significantly reduced the expression of rate-limiting enzymes for lipid synthesis and the expression of involucrin and small proline-rich proteins, which may explain the disturbed restoration of functional stratum corneum layers following betamethasone treatment (67). Corticosteroids may exert a more potent anti-inflammatory effect, but may impair skin barrier restoration (67).

Specific targeting of the four described histamine receptors (H1R – H4R) is an emerging strategy for achieving AD control. Although H1R antagonists are commonly used to treat AD, the efficacy is poor (53). The treatment strategy of combining a H1R antagonist with a H4R antagonist was assessed in a murine dermatitis model. Administration of the H4R antagonist JNJ777120 attenuated scratching and improved dermatitis, as assessed by clinical scores, pathology, and cytokine levels in skin lesions (73). The effects were augmented by combined treatment with the H1R antagonist olopatadine, having similar therapeutic efficacy to prednisolone (73). Combined targeting of H1R and H4R may significantly reduce chronic dermatitis by synergistic inhibition of pruritus and skin inflammation (73).

Acupuncture may exhibit significant effects on experimental itch. A patient- and examiner-blinded, randomized, placebo-controlled, crossover trial evaluated the efficacy of acupuncture and the antihistamine cetirizine in a temperature-modulated itch model involving 20 AD patients (74). The mean itch intensity was significantly lower following verum acupuncture com-

pared with placebo acupuncture, cetirizine, placebo cetirizine, or no-intervention control ($P < 0.05$). Verum acupuncture and cetirizine were significantly superior to their respective placebo interventions regarding itch ($P < 0.05$). The flare size following verum acupuncture was smaller ($P = 0.034$) than following placebo acupuncture (74). Cetirizine and verum acupuncture significantly reduced type I hypersensitivity itch in patients with AD. Concurrent acupuncture was more effective than preceding acupuncture, possibly because of counter-irritation or distraction (74).

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors, which regulate proliferation, differentiation, and immune responses of cells (75). Activators of the PPAR α , PPAR β , and PPAR γ isoforms were applied on inflamed skin in a mite-antigen-induced murine AD model. Only the topical application of PPAR α activator, but not activators of PPAR β and PPAR γ , improved clinical dermatitis, reduced inflammatory cell infiltration in the dermis, and alleviated the increase in serum IgE levels (75). PPAR α expression was downregulated in murine epidermis, as seen in AD patients. Topical PPAR α activators could become a therapeutic agent for AD (75).

In the future, possible disease-modifying strategies will enter routine use in the management of AD and may achieve the goal to stop or even reverse the development of atopic comorbidities (16).

Contact dermatitis

Contact allergy surveillance networks provide information to a multitude of stakeholders, which is indispensable for evidence-based decision-making in the field of prevention (76). Methods and results of the German contact allergy surveillance network including 56 Departments of Dermatology have recently been reviewed, demonstrating decreasing chromate reactions or increasing epoxy resin reactions (76). National prescription data of drugs and statistics of labeling of preservatives on cosmetics can be included in the analyses and allow risk estimates for specific allergens (76).

Another study addressed the association between contact sensitization, AD, and asthma in clinical databases from Denmark (77). An inverse association was found between contact sensitization and presumed severe AD (OR, 0.70; 95% CI, 0.61–0.81) or asthma (OR, 0.61; 95% CI, 0.42–0.90). Sensitization to fragrances and topical drugs was positively associated with AD, whereas all groups of chemicals and metals showed inverse associations (77). Patients with severe AD and asthma have an overall lower prevalence of contact sensitization when compared with controls. Mild-to-moderate disease does not suppress contact sensitization (77).

A retrospective analysis of clinical data, patch test results, and sensitization sources was undertaken at the Leuven Department of Dermatology to determine the frequency, clinical presentation, and cross-reactivity patterns for allergic reactions following systemic administration of corticosteroids among patients with identified and investigated 'contact allergy' to corticosteroids (78). Sixteen of 315 patients with CS delayed-type hypersensitivity presented with allergic

manifestations following systemic corticosteroid use. The majority of reactions was interpreted as 'systemic contact dermatitis' due to oral or parenteral re-exposure of presensitized individuals initially sensitized by topical application (78). As most patients seem to be able to react to any corticosteroid molecules, a systematic individualized evaluation of their sensitization and tolerance profile is mandatory (78).

Cannabis sativa and its active constituent 9-tetrahydrocannabinol (THC) exert the biological effects dependent and independent of G-protein-coupled CB1 and CB2 receptors (79). In a DNFB-mediated allergic contact dermatitis model, topical THC decreased ear swelling, myeloid immune cell infiltration, IFN- γ production by T cells, and CCL2 production by keratinocytes in wild-type and CB1/2 receptor-deficient mice (79). Future strategies may harness cannabinoids for the treatment of inflammatory skin diseases.

Urticaria

Chronic spontaneous urticaria (CU) has a point prevalence of 0.5–1% of the population and a high socioeconomic impact on direct and indirect healthcare costs (80). Psychosocial factors are estimated to contribute to the pathogenesis and exacerbation of CSU in about half of the cases according to a recent systematic review (81).

According to a consensus report of the Global Allergy and Asthma European Network, patient-reported outcomes should be used in clinical trials and routine practice for the evaluation of urticaria patients and actually be considered as the primary outcome of future clinical trials (82). The Chronic Urticaria Questionnaire on Quality of Life, CU-Q(2)oL, was specifically developed and validated for the investigation of patients with CU. It is available in many languages (82).

Nonsedating H1R antagonists are the mainstay of symptomatic therapy, but effective in <50% of patients. Although guideline-recommended up dosing up to fourfold increases symptom control, new therapeutic strategies are needed (80). Up dosing of nonsedative antihistamines up to fourfold may also work in cold contact urticaria without sedation, as recently shown in a randomized, crossover, double-blind, placebo-controlled 12-week study with the nonsedating H1R antagonist bilastine (83). The anti-IgE antibody omalizumab could be another worthwhile treatment option for CU (84). Evidence from Japan indicates that about one-third of CU patients not controlled by oral H1R antagonists will spontaneously be cured after one year, whereas about two-third will have lost their symptoms after 5 years (85).

Thrombin generation through the extrinsic coagulation pathway has been linked to CU previously. Increased blood coagulation potential with involvement of intrinsic coagulation factors has recently been shown in CU, which may contribute *in vivo* to the generation of fibrin even by small amounts of thrombin (86).

The differential diagnosis of CU involves urticaria vasculitis and autoinflammatory disorders like cryopyrin-associated periodic syndrome and Schnitzler's syndrome (87). Using a symptom-based diagnostic algorithm for management of patients with wheals or angioedema may help physicians

diagnosing CU in a cost- and time-effective way (88). Systemic symptoms including recurrent fever attacks, arthralgia or arthritis, and fatigue in patients presenting with an urticarial rash should raise a suspicion of autoinflammatory disorders. Clinical clues and tips for identifying and managing patients presenting with a chronic urticarial rash (Fig. 2) have recently been published (87).

Autoimmune urticaria is caused by histamine-releasing autoantibodies against Fc ϵ RI α , which induce histamine release from basophils and MC, but functionality and immunoreactivity of these antibodies do not correlate well (89). Approximately 25% of all CU patients have a positive basophil histamine release assay and a positive autologous serum skin test, whereas 50% are negative regarding both. The functionality of CU sera appears to be complement dependent on MC, and basophil activation by CU sera is predominantly restricted to IgG1 and IgG3 subclasses (89). A new 'gold standard' for the diagnosis of autoimmune CU consisting of positive autoreactivity, functional bioassay, and functional immunoassay has been proposed (89).

Permeabilizing and histamine-releasing activity of sera from 19 patients with CU and 11 healthy blood donors was evaluated regarding serum-induced degranulation of two MC lines either expressing or lacking Fc ϵ RI (90). Thereby, 85% of autologous serum skin-test-negative sera induced MC degranulation. Endothelial cell leakage remained unchanged after immunoglobulin depletion and was prevented by antihistamine, platelet-activating factor, or leukotriene antagonist. The degranulation of MC through an immunoglobulin-independent mechanism by CU sera should be particularly relevant in patients without circulating autoantibodies to Fc ϵ RI α or IgE (90).

Drug-induced urticaria with cross-intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) should also be investigated for paracetamol intolerance: A recent trial from Spain evaluating 252 patients with urticaria or angioedema caused by cross-intolerance to NSAIDs showed that ibuprofen was the most commonly implicated drug, followed by acetylsalicylic acid (91). The authors conclude that selective COX-2 inhibitors may be unsafe in these patients if they are also intolerant to paracetamol. Selective COX-2 inhibitors should be administered as a controlled, incremental dose provocation test to assess tolerance (91).

Drug reactions

In drug rash with eosinophilia and systemic symptoms (DRESS, also known as drug-induced hypersensitivity syndrome DIHS), a reactivation of latent human herpesvirus (HHV)-6 with fever and hepatitis is frequently observed (92). Recent study results suggest that CD11b-expressing monomyeloid precursors harboring HHV-6 are invading the skin following chemoattraction by high-mobility group box (HMGB)-1 released from damaged skin. They infect skin-resident CD4(+) T cells with HHV-6 *in loco* (92). Therefore, the primary site of HHV-6 reactivation during DRESS seems to be the skin.

The Drug Hypersensitivity Interest Group of the EAACI has published their 2013 expert opinion paper including

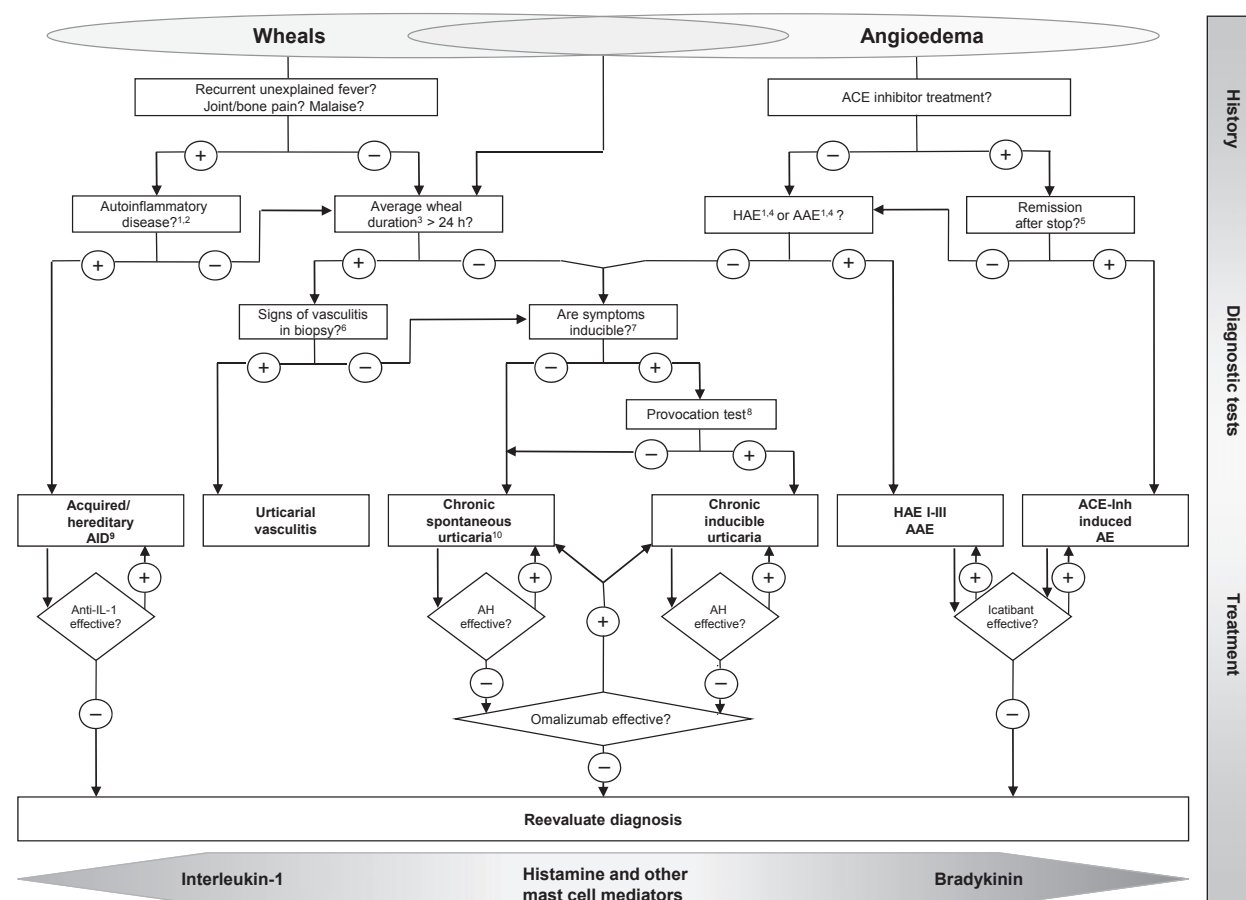


Figure 2 Management of patients presenting with wheals or angioedema (from Maurer et al., ref. 88). This algorithm for patients with wheals or angioedema was published by Maurer et al. in *Allergy*, 2013 (ref. 88). Specific questions and tests should be asked or performed during the workup, as indicated by the numbers in the diagram: (1) Patients should be asked for a detailed family history and age of disease onset. (2) Test for increased inflammation markers (C-reactive protein, erythrocyte sedimentation rate), test for paraproteinemia in adults, look for signs of neutrophil-rich infiltrates in skin biopsy; perform gene mutation analysis of hereditary periodic fever syndromes (e.g., cryopyrin-associated periodic syndrome), if strongly suspected. (3) Patients should be asked: 'How long do your wheals last?' (4) Test for complement C4 levels and C1-INH levels and function; in addition, test for C1q and C1-INH antibodies, if AAE is suspected; carry out gene mutation analysis, if former tests are unremarkable, but patient's history suggests hereditary angioedema. (5) Wait for up to 6 months for remission; additional diagnostics to test for C1 inhibitor deficiency should only be performed, if the family history suggests hereditary angioedema. (6) Does the biopsy of lesional skin show damage of the small vessels in the papillary and reticular dermis and/or fibrinoid deposits in perivascular and interstitial locations suggestive of UV? If yes, direct immunofluorescence should be performed to look for immune complexes (immunoglobulins or complement) in

vessel walls. Also, if suggested by the history, systemic vasculitic diseases that may present with UV (e.g., lupus erythematosus or Sjögren's syndrome) should be ruled out and patients should be screened for antinuclear and extranuclear antibodies where indicated. (7) Patients should be asked: 'Can you make your wheals come?' (8) In patients with a history suggestive of inducible urticaria, standardized provocation testing according to international consensus recommendations should be performed. (9) Acquired AIDs include Schnitzler syndrome as well as systemic-onset juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD); hereditary AIDs include cryopyrin-associated periodic syndromes (CAPS) such as familial cold autoinflammatory syndromes (FCAS), Muckle-Wells syndrome (MWS), and neonatal onset multisystem inflammatory disease (NOMID), more rarely hyper-IgD syndrome (HIDS) and tumor necrosis factor receptor alpha-associated periodic syndrome (TRAPS). (10) In some rare cases, recurrent angioedema is neither mast cell mediator mediated nor bradykinin mediated, and the underlying pathomechanisms remain unknown. These rare cases are referred to as 'idiopathic angioedema' by some authors. (AAE: acquired angioedema due to C1 inhibitor deficiency; ACE-Inh: angiotensin-converting enzyme inhibitor; AE: angioedema; AH: antihistamine; AID: autoinflammatory disease; HAE: hereditary angioedema; IL-1: interleukin-1)

extensive literature review on desensitization procedures in delayed drug hypersensitivity reactions (93). Published success rates for sulfonamide hypersensitivity in HIV-positive patients or antibiotic hypersensitivity in patients with cystic fibrosis reach 80%. Desensitization in delayed hypersensitivity reactions is mostly restricted to mild, uncomplicated exanthemas and fixed drug eruptions, with highly variable success rates (93). Slower protocols tend to be more effective than rush protocols. The decision to desensitize a patient must follow an individualized risk–benefit evaluation (93).

A prospective, observational, longitudinal study from Spain involving 189 intravenous rapid desensitizations for antineoplastic agents has evaluated a new rapid desensitization protocol for safety and efficacy (94). No breakthrough reactions occurred in 94% of desensitizations, and most breakthrough reactions were mild. In 10 oxaliplatin-reactive patients, 38 desensitizations were successfully accomplished (94). Sensitivity for oxaliplatin-specific IgE was 38% (0.35 UI/l cutoff point) and 54% (0.10 UI/l cutoff point); specificity was 100% for both cutoff points. The new protocol was effective for oxaliplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide, and rituximab (94).

The French–Belgian Allergy Vigilance Network reported 333 severe anaphylactic reactions observed from 2002 to 2010 analyzed for clinical signs, causative drugs, and efficacy of diagnostic procedures (95). Anaphylactic shock (76.6%), severe systemic reactions (10.5%), acute laryngeal edema (9%), severe bronchospasm (2.1%), and six fatal cases (1.8%) were documented; 63 cases (18.9%) occurred during anesthesia (95). Identified causative drugs included (mostly beta-lactam-) antibiotics (49.6%); muscle relaxants, latex, and anesthetics (15%); nonsteroidal anti-inflammatory drugs (10.2%); acetaminophen (3.9%); resonance imaging contrast media (4.2%); and immunotherapy and vaccines (3.9%). Skin tests confirmed most diagnoses (95), even if skin testing with drug allergens, and especially beta-lactams, is not risk free (96). The recently reviewed various *in vitro* test systems for drug allergy might provide additional or alternative evidence (97). This is even more important in drugs like quinolones, where skin testing induces false-positive results. Sepharose radioimmunoassays and basophil activation tests may help diagnosing those patients (98).

Multiple drug hypersensitivities (MDHs) are observed in up to 10% of patients with severe immune-mediated drug hypersensitivity reactions (99). Different T-cell subpopulations, especially Treg cells, were functionally analyzed by

depleting and selectively re-adding them in an experimental study involving MDH patients, single-drug-allergic patients, and healthy controls. No functional deficiency of Treg cells was observed in all drug-allergic patients (99). The drug-reactive T cells of the MDH patients were found in an *in vivo* pre-activated T-cell fraction and may show a lower threshold for activation by drugs.

An association of atopy with immediate-type beta-lactam allergy was confirmed in a recent trial involving 340 patients and 340 controls from Spain (100). Total serum IgE and mite-specific IgE were significantly higher in beta-lactam-allergic patients. The beta-lactam-specific IgE decreased slower over time in atopic than in nonatopic patients (100). The demonstrated association between nucleotide-binding oligomerization domain (NOD) gene polymorphisms and beta-lactam allergy mirrors the influence of these polymorphisms on beta-lactam allergy (101).

A recent telephone questionnaire study determined the predictive value of negative re-challenge under hospital surveillance for 637 patients with cutaneous drug reactions (102). Ninety percent of these patients had a good tolerance to subsequent treatment with the previously rechallenged drug (102).

In conclusion, clinical trials and experimental work of the last few years have broadened our knowledge on various aspects of AD and skin allergies. Time will show whether emerging therapies such as biologics for AD and CU will be as beneficial for our patients as expected.

Author contributions

AW and KF have performed literature search and written the manuscript.

Conflicts of interest

AW has received lecture honoraria and has performed clinical trials sponsored by or is a paid consultant for ALK-Schering, Amgen, Astellas, Basilea, Bayer, Biocon, Galderma, GlaxoSmithKline, Hickma, Janssen, Karrer, L'Oreal, MEDA, Merck-Sharp-Dohme, Novartis, Pierre-Fabre, Roche, and Therakos.

KF declares that there is no conflicts of interest regarding this manuscript.

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