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Looking Ahead in Dermatology: Skin and Allergy

J. Ring, B. Belloni and H. Behrendt

Department of Dermatology and Allergology Biederstein. ZAUM – Zentrum Allergie und Umwelt (Center for Allergy and Environment). Technische Universität München.

Abstract. The prevalence of allergic diseases has increased tremendously over the last decades. Clinically they comprise a spectrum of many different conditions caused by specific immunological hypersensitivity in response to a mostly apathogenic substance. Environmental factors such as lack of immune-stimulating contacts (infection, vaccination) and exposure to allergy-enhancing anthropogenic pollutants from tobacco smoke or traffic exhaust particles are suspected to be involved in the increase of allergies. Recently it has been shown that pollens are not only allergen carriers but also secrete highly active proinflammatory lipid mediators, pollen-associated lipid mediators (PALMs), which have proinflammatory and immuno-modulatory capacity that facilitates allergic sensitization of the skin and mucous membranes.

The skin is one of the most important organs where allergic reactions manifest. Many different morphological and physiopathological entities can be observed in the skin that represent all kinds of pathogenetic immune reactions from immediate-type allergy, urticaria, angioedema, anaphylaxis, cytotoxic and immune complex reactions such as thrombocytopenic purpura or allergic leukocytoclastic vasculitis, exanthematous drug eruptions, granulomatous skin reactions to tattoos or fillers as well as a wide spectrum of dermatitis and eczema with allergic contact dermatitis being one of the most common occupational diseases in many countries.

Recent progress in pathophysiology has revealed a role of epidermal barrier function as well as immunodeviation in atopic eczema giving rise to new diagnostic and therapeutic strategies.

The interdisciplinary character of allergy implies a close cooperation between different disciplines where dermatology plays a major role in the management of allergic diseases, covering diagnostic, therapeutic and preventive aspects.

Key words: allergy, allergic skin disease, urticaria, angioedema, anaphylaxis, purpura, vasculitis, contact dermatitis, atopic eczema, drug eruptions, granulomatous reactions.

MIRANDO HACIA EL FUTURO EN DERMATOLOGÍA: PIEL Y ALERGIA

Resumen. La prevalencia de las enfermedades alérgicas ha aumentado tremendamente en las últimas décadas. Clínicamente abarcan un espectro de diferentes entidades que están causadas por una hipersensibilidad inmunológica específica como respuesta a una sustancia, en general, no patógena. Se sospecha que el aumento de las alergias se debe a factores ambientales como la falta de contactos que estimulen el sistema inmunitario (infección, vacunas) y la exposición a contaminantes antropogénicos que intensifican las alergias como el humo del tabaco o las partículas de combustión. Recientemente se ha demostrado que los pólenes no son solo portadores de alérgenos, sino que también segregan mediadores lipídicos altamente proinflamatorios, mediadores lipídicos asociados al pólen (siglas en inglés PALM), que facilitan la sensibilización alérgica de la piel y las membrabas mucosas por su capacidad proinflamatoria e inmunomoduladora.

La piel es uno de los órganos más importantes donde se manifiestan las reacciones alérgicas. En la piel se pueden observar diferentes entidades morfológicas y fisiopatológicas que representan todos los tipos de reacciones inmunitarias patogénicas desde alergia inmediata, urticaria, angioedema, anafilaxia, reacciones citotóxicas y mediadas por inmunocomplejos como la púrpura trombocitopénica o la vasculitis leucocitoclástica, toxicodermias exantemáticas, reacciones cutáneas granulomatosas por tatuajes o rellenos así como un amplio espectro de dermatitis y eccema, siendo la dermatitis alérgica de contacto una de las enfermedades profesionales más frecuentes en muchos países.

Los recientes avances en la fisiopatología han revelado un rol de la función de la barrera epidérmica así como una desviación inmunitaria en el eccema atópico, lo que da lugar a nuevas estrategias diagnósticas y terapéuticas.

El carácter interdisciplinar de la alergia implica una estrecha colaboración entre diferentes disciplinas donde la dermatología tiene un papel principal tanto en el diagnóstico, el tratamiento como en la prevención de las enfermedades alérgicas.

Palabras clave: alergia, enfermedad alérgica cutánea, urticaria, angioedema, anafilaxia, púrpura, vasculitis, dermatitis de contacto, eccema atópico, toxicodermias, reacciones granulomatosas

Correspondence:
Johannes Ring
Department of Dermatology and Allergology Biederstein
Klinikum rechts der Isar, Technische Universität München
Biedersteiner Str. 29
80802 Munich. Germany
johannes.ring@lrz.tum.de

Table 1. Allergic diseases

Rhinoconjunctivitis ("hay fever")
Asthma
Eczema (atopic ezcema)
Urticaria
Angioedema (Quincke)
Anaphylaxis
Gastroenteritis
Agranulocytosis (and other cytopenias)
Serum sickness (arthralgia, fever, nephritis etc)
Contact dermatitis
Drug eruptions
Granulomas

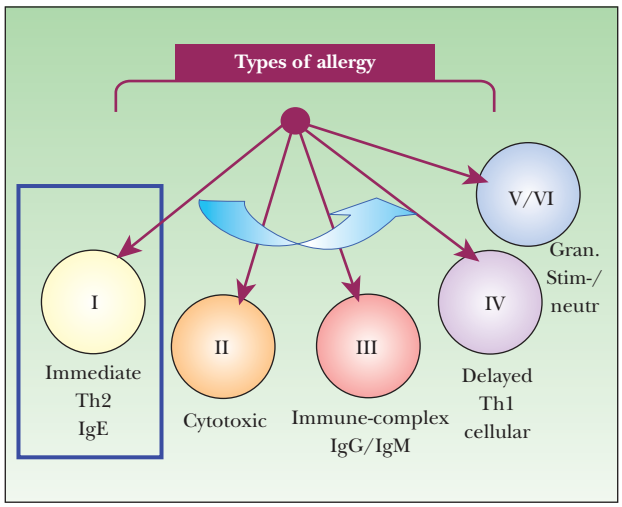

Figure 1. Types to allergic immune reactions according to Coombs and Gell. Modified by Ring[3].

Introduction

Allergic diseases have been known for centuries in medical history. One of the earliest individual descriptions may concern Imperator Octavianus Augustus who probably suffered from asthma, hay fever and eczema with other family members possibly also being atopic[1]. The term "allergy" itself was created in 1906 by the Viennese pediatrician Clemens von Pirquet when he wanted to bring some order into the newly developing field of immunology, trying to distinguish between harmful and protective immunity; von Pirquet described allergy as an altered reactivity in a very broad sense[2]. Today allergy is defined as *"immunologically mediated hypersensitivity leading to disease"*[3]. Since von Pirquet's era major progress has been made in the understanding of allergic reactions[3].

Table 2. Hypothetical concepts to explain increase in prevalence of atopic diseases[3]

Increased awareness and improved diagnostics
Genetic susceptibility
Psycho-social influences
Allergen exposure
Decreased stimulation of the immune system ("jungle" or "hygiene" hypothesis)
Underlying disease
Iatrogenic (antihistamines, antiacids?)
Environmental pollution (type II)
Climate change

Clinically allergic diseases describe a spectrum of many different conditions caused by specific immunological hypersensitivity in response to mostly apathogenic substances from the environment (table 1). Allergy, therefore, is the "environmental disease number one"! Many organs can be affected by allergic reactions; most commonly allergy affects the skin and the mucous surfaces, i.e. the frontiers where the individual is in direct contact with the environment[3].

Pathophysiologically the classification of Coombs and Gell from 1963 is still valid for didactic reasons and describes different pathogenic immune reactions leading to disease. Most commonly and in some countries, especially in the USA, allergy is mostly regarded as immunoglobulin E reaction. Some people proposed that the American Academy of Allergy should change its name into "Academy of IgE-ology". It has to be remembered that many other diseases and many other pathogenic mechanisms are involved in allergy (fig. 1).

Epidemiology of Allergic Diseases

While allergic diseases were not so common at the beginning of the 20th century, there has been a tremendous rise in prevalence since the 1950ies and 1960ies, especially with regard to atopic diseases. They have increased in prevalence up to 10-20% for hay fever, 2-5% for bronchial asthma, 10-20% for atopic eczema in children (3-5% in adults), contact dermatitis 5-15%. The reasons for this increase are not clearly established; however, there are a variety of hypothetical concepts (table 2).

The very popular "jungle" or "hygiene" hypothesis focuses on decreased immune stimulation, decreased parasite

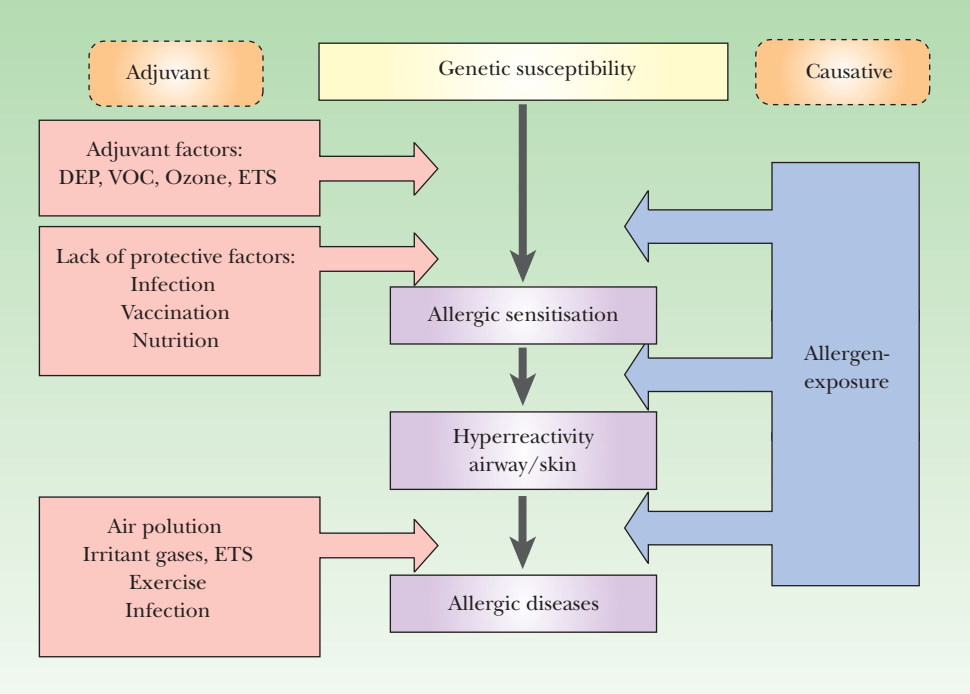

Figure 2. Determinants of allergic inflammation. Behrendt, 2000.

infestation through improved hygienic measures going along with increased prevalence of allergic diseases.

There is some evidence that the hygiene hypothesis holds true for respiratory atopy and that children growing up on a farm or having suffered from increased rates of infection early in life seem to have fewer atopic diseases[4-6]. There is the opposite effect with atopic eczema and there is not only no protection, but some studies found even increased prevalence rates[6-8].

Another hypothesis focuses on the role of environmental pollutants (fig. 2): it has been shown that indoor pollution, especially tobacco smoke, leads to an increase in prevalence of atopic eczema in children with a genetic predisposition[9]; the urinary cotinin concentration as a measure of exposure was correlated to actual atopic eczema.

Indoor pollutants as volatile organic compounds (VOCs) have shown to lead to disturbances of skin barrier function[10] and increased atopy patch test reactions when individuals were placed in a climate chamber: the addition of a non-toxic mixture of VOCs led to a marked increase of intensity of atopy patch test reactions against house dust mite[11].

In the outdoor situation it is the exposure to traffic exhaust which is directly correlated with an increased prevalence of atopy and also atopic eczema[12,13].

It has been shown that Diesel exhaust particles can lead to increased IgE formation and Th2 shift in mice experiments and human studies[14,15].

Furthermore pollen are not only allergen carriers, but secrete highly active pro-inflammatory lipid mediators (pollen-associated lipid mediators [PALMs]) which help to prepare the surface of the skin or the mucous membrane and facilitate allergic sensitization[16-18].

In the following, examples of allergic diseases will be briefly discussed with regard to modern developments.

Urticaria, Angioedema and Anaplyhaxis

Urticaria and angioedema often are the first symptom of anaphylaxis. In the acute development of urticaria it cannot be predicted whether the reaction proceeds to a severe life-threatening reaction involving the cardiovascular and respiratory system; so the severity grading of anaphylactic reactions according to Ring and Messmer describes skin involvement as grade I (table 3).

Often individuals with clear sensitization in skin prick test (SPT) or radio-allergo-sorbent Test (RAST) only experience severe reactions under very defined special conditions, e.g. when they have an infection, when they have exercised physically, have undergone psychological stress or taken medication, such as beta-blockers or non-steroidal antiinflammatory drugs (NSAIDs). This phenomenon has been called "summation" or "augmentation" anaphylaxis and is probably much more common than previously thought[19].

A special example of exercise-induced anaphylaxis elicited by food allergens is the newly discovered form of wheat allergy, where individuals have IgE-antibodies against a specific protein of wheat, namely Omega-5 gliadine as "wheat-dependent exercise induced anaphylaxis (WDEIA)"[20].

Table 3. Severity grading of anaphylactic reactions according to Ring and Meßmer 1977

Grade	*Symptoms observed*			
	Skin	*Gastrointestinal*	*Respiratory*	*Cardio-vascular*
I	Itch Flush Urticaria Angioedema	–	–	–
II	" (not obligatory)	Nause Cramps	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia (> 20/min) RR changes (> 20 mmHg syst) Arrhytmia
III	" (not obligatory)	Vomitus Defecation	Laryngeal edema Bronchospasm Cyanosis	Shock
IV	" (not obligatory)	"	Respiratory arrest	Cardiac arrest

The future will show that specific antibodies of the IgE class against individual allergens will have a very high impact in prognosis with regard to severe anaphylactic reactions as soon as they are available in the recombinant form, similarly for the gly m 4 for soy bean allergy or Ara h8 for peanut anaphylaxis.

New developments were found for the simultaneous occurrence of mastocytosis and allergy. Mastocytosis seems to be much more common than generally thought. Often individuals only have minor skin lesions or can only be diagnosed by elevated levels of serum tryptase. These individuals also have an increased risk for anaphylaxis[21].

New developments in chronic urticaria can be seen in the autologous serum test developed by Malcolm Greaves (Greaves' test) where autologous serum is injected intradermaly (1:10 or 1:100 dilution!) and an urticarial skin lesion develops[22]. Often, this positive Greaves' test goes along with antibodies against IgE or against the high affinity Fcϵ-receptor (FcϵRI).

Also contact urticaria can progress to more severe reactions called contact anaphylaxis[23] as we have recently observed in a case with urticaria and anaphylaxis after topical application of Diclofenac gel (Kerzl, Ring, in prep.).

Purpura and Vasculitis

While the type-II reactions as allergic thrombocytopenic purpura are rather rare, leukocytoclastic vasculitis is a common problem in clinical medicine. It can be elicited by infection, neoplasia, but also by food allergens and additives. Recently we observed a case of food-induced leukocytoclastic vasculitis which was positive in the oral provocation test. The patient was reacting against kiwi and developed petechial rashes on the trunk, legs and forearm 6-10 hours after oral provocation with kiwi. In the dermatopathology of a purpuric lesion leukocytoclastic vasculitis was seen together with immunoglobulin deposits. In the immunoblot there was a strong IgG reaction specific against Act c 1 as major allergen of kiwi (Actinidin)[24].

Allergic Contact Dermatitis

Allergic contact dermatitis seems to be much more common than previously thought. Usually, when studying positive patch tests in dermatology departments, rates of ca. 15 % for nickel or fragrances can be found. Surprisingly similar rates have been found in an epidemiological trial comprising a representative population of the city of Augsburg in Bavaria (KORA Study) with a prevalence of 13 % nickel and 15,9 % fragrance-mix[7].

Unfortunately the technology of diagnostic tools in contact dermatitis is not very advanced. In principle we are using the same "patch test" ("Läppchen-Test") as it was first used and described by Josef Jadassohn in 1895[25]! Some progress has been achieved by the introduction of Finn chambers by Pirilä in different sizes and the thin layer rapid use epicutanous test, the TRUE test[26].

New findings have been observed with regard to systemically induced allergic contact dermatitis (also called hematogenous contact dermatitis) on the field drug reactions. We have seen systemic reactions after epicutaneous testing with tetrazepam in a case with dyshidrotic palmoplantar lesions after oral provocation (Ring, in prep.).

The newly described symmetrical "drug-related intertrigenous and recurrent flexural exantema" (SDRIFE) can be regarded as a subgroup of this entity with a nicer name than the common "baboon syndrome"[27].

Table 4. Exanthematous drug eruptions: elicitors

Acneiform eruptions	EGF-R-antagonists, steroids
AGEP	Antibiotics, chloroquin
Alopecia	Chemoterapy
Angioedema	ACE inhibitors
Aphthous stomatitis	Methotrexate
Bullous eruptions	Sulfonamides, anticonvulsants
Contact dermatitis	Antibiotics, bufexamac
EEM	Allopurinol, anticonvulsants
E nodosum	Contraceptives
Fixed drug eruption	Tetracyclin, hydroxyurea
Hyperpigmentation	Bleomycin, amiodarone
Lichenoid eruption	Gold, sulfamides
Maculopapular eruption	
Nail dystrophy	Chemoterapy
Phototoxic reaction	Antibiotics (tetracyclin)
Pruritus	Hydroxyethylstarch
Pseudoporphyria	Sulfonamides, contraceptives
Psoriasis	β-bloquers
Lyell's S., TEN	Allopurinol, sulfonamides
Urticaria, angioedema	Aspirin, opiates, antibiotics
Vasculitis	Methotrexate, hydroxyurea

Exanthematous Drug Eruptions

The field of exanthematous drug eruptions is very complex both in morphology and pathophysiology (table 4). Often the mechanisms are unclear. Sometimes there is no clear history for earlier sensitization which is a prerequisite of allergy. The new concept proposed by Werner Pichler of pharmacological interaction with immune receptors (PI Concept) is very attractive; according to the concept, drugs bind directly to an immune receptor - like superantigens - and thus activate immune cells imitating an immune response without developing a specific sensitization[28].

Allergic reactions to corticosteroids have been described and can be tested both in the patch test, but also in the oral provocation test.

Progress has been made in the field of radiographic contrast media hypersensitivity where the non-ionic compounds can elicit so-called delayed reactions with skin rashes which are most likely T-cell mediated and can be tested by patch test, but also intradermal test with readings after 24 and 48 hours[29].

What is really missing, is an in-vitro-test for contact allergy like we have it for IgE-mediated reactions with the RAST! So many patients with generalized eczema cannot be diagnosed, because either they are treated with steroids which excludes testing or they are clinically exacerbated and therefore cannot be tested. The future might offer a chance using tetramere technology to detect specific CD4 or CD8 T cells.

Atopic Eczema

Atopy occurs in families on the basis of a genetic background. Many chromosomes and genes have been described as being involved in signs and symptoms of atopy or atopic diseases[30]. Recent progress focused on mutations in the filaggrin gene as a causal factor in ichthyosis vulgaris and a major pre-disposing factor for early on-site atopic eczema with allergic sensitization[31,32]. Filaggrin develops through proteolysis from pro-filaggrin and plays a major role in the forming of the cornified envelope, putting together keratin filaments and lipids in the stratum corneum. When filaggrin is mutated, disturbance of the epidermal barrier function occurs. Filaggrin also plays a role as natural moistureising factor. One out of 15 European individuals carries at least one filaggrin-null mutation leading to an increased risk for atopic eczema[33] (fig. 3).

New studies focus on adult atopic eczema which was neglected in earlier years. Many physicians are regarding atopic eczema simply as a childhood disease. However, only one third of children affected with AE "will grow out" of the disease, while two thirds will suffer from AE later in life[34].

Besides this persisting atopic eczema newly developing disease is observed in adults. There are few epidemiological trials, but some studies show prevalence rates of 3-10% of adult atopic eczema[35,36].

A new development is the atopy patch test where IgE-inducing allergens are applied topically to untreated non-lesional skin and the development of eczematous skin lesions is read after 24 - 72 hours[37,38].

APT has a lower sensitivity, but much higher specificity (80-90%) than SPT or RAST: this means that with this test the relevance of an IgE-mediated sensitization for the eczematous skin disease can be evaluated.

Psychology and Skin Allergy

It is well known that psychological factors can influence skin diseases, especially allergic skin diseases like urticaria or eczema. However, the mechanisms are not well understood. The major symptom of allergic skin diseases is itch which can be visualized using positron emission tomogra-

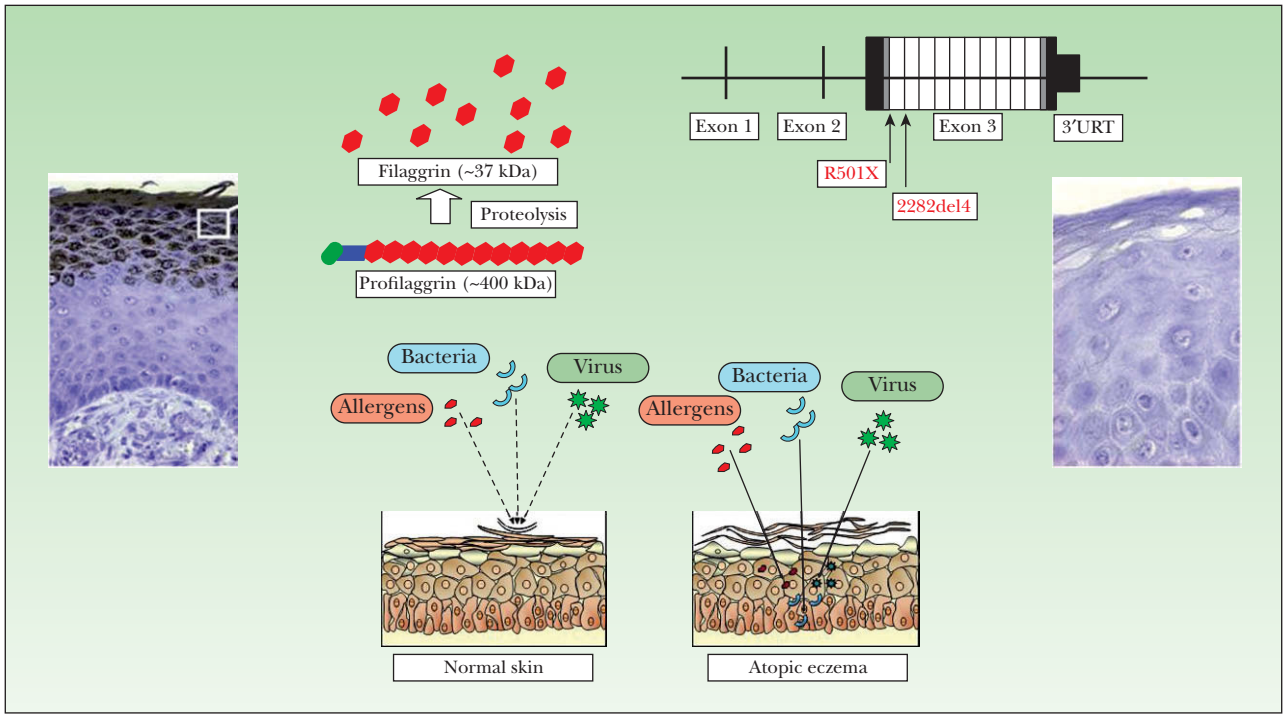

Figure 3. Filaggrin mutations as a major character and factor in the formation of a disturbed epithelial barrier function in atopic eczema (According to Weidinger et al).

phy (PET) or functional magnetic resonance imaging (MRI)[39]. In the future different activation and suppression patterns might allow better understanding of central nervous mechanisms and give way to new therapeutic modalities.

It is well known that psychological factors can trigger exacerbations of eczema. Especially in childhood eczema, family dynamics play a major role as has been shown in many studies. We found that children suffering from atopic eczema have the feeling of an over-dominant mother with a rather rigid educational style, while the father seems "too small" and too far away in the view of the child[40].

Recent studies have shown that family life events influence the development of atopic eczema: where there was severe disease (cancer or a severe accident) in the family, the risk of the child was significantly lower (OR: 0,29) to develop eczema. On the other hand, when the parents were constantly quarreling, separating or divorced, this led to a massive increase in risk (OR: 3,59) for the child to develop atopic eczema[41].

These complex interactions both at the somatic and the psychological level have to be taken into account in our management programs of this disease. Therefore educational programs have been developed ("eczema school") which contain not only medical information transfer, but also psychosocial teaching of self-perception, coping strategies within the itch-scratch behavior and teaching social competence training and stress reduction techniques together with nutritional recommendations for adequate diets avoid unnecessary eliminations[42]. This educational program has been validated and studied in a controlled randomized trial and found to be significantly effective.

Novel Treatments

While in other skin diseases – as e.g. psoriasis – there has been a tremendous wave of innovation by the new biologics, namely anti-TNF or anti-T-cell strategies (Infliximab, Etanercept, Adalinumab, etc.), only little impact in the field of allergic skin diseases by these compounds can be observed. Anti-IgE has been registered for moderate to severe asthma and has been tried in atopic eczema in some case reports and pilot studies. We have reported some effect in very severe cases of atopic eczema and very high IgE levels; we think the mechanism of anti-IgE in eczema cannot only be the removal of the IgE-antibodies in the serum, but rather a regulatory effect, probably on the B cell level[43,44].

Anti-Interleukin-5 antibodies have also been tried since eosinophils are a predominant characteristic of atopic inflammation. Mepolizumab has been proven to have a significant, but only moderate effect in atopic eczema with two injections[45]. Significant effects of Mepolizumab have been observed in hypereosinophilic symptom (HES)[46,47].

There are case reports of other biologics, namely Alefacept, Efalizumab, in atopic eczema, but no controlled trials[48].

Table 5. Different pathogenic immune reactions underlying various allergic skin diseases

Clinical manifestations	*Possible pathomechanism*
Urticaria	IgE, serum sickness (type I)
Purpura (thrombopenic)	Cytotoxic (type II)
Purpura (vasculitis)	Immune-complex (type III)
Atopic eczema	IgE + Th2 (type I + IVb)
Allergic contact dermatitis	Th1 (type IVa)
Maculopapular exanthema	Type IV
Exfoliative dermatitis	Type IVa (CD4)
Acute generalized exanthematic pustulosis	Type IVd (Th17)
Lymphohistiocytosis infiltration	Type IV?
Vesiculo.bullous and fixed drug eruption	Type IVc (CD8)
Toxic epidermal necrolysis/ Lyell's syndrome)	Type IVc (CD8)?
Granulomatosis reaction (e.g. vobine collagen)	Type V
Autoimmune urticaria	Type VI?

The skin is one of the most important manifestation organs of allergic reactions.

Rituximab, the anti-B-cell antibody (anti-CD20), has shown to be effective, but not without side effects[49].

Anti-inflammatory treatment is the mainstay of therapy for both allergic dermatitis and atopic eczema. It includes topical corticosteroids as well as topical calcineurin-inhibitors such as tacrolimus and pimecrolimus. Phototherapy or photochemotherapy may serve as an adjuvant modality. In severe cases, immunosuppression has to used (Cyclosporin A).

Conclusion and Outlook

The skin is one of the most important manifestation organs of allergic reactions (table 5). Many different morphological and pathophysiological entities can be observed in the skin. All kinds of pathogenic immune reactions can lead via quite different pathomechanisms to a variety of allergic skin diseases.

The interdisciplinary character of allergy implies a close cooperation between different disciplines in the management of these patients. Dermatology plays a major role in managing allergic diseases, be it from the diagnostic, therapeutic or preventive aspect.

Conflicts of interest
Authors have no conflicts of interest to declare.

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