EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

GLOBAL ATLAS OF SKIN ALLERGY

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Editors

Knut Brockow
Charlotte G. Mortz

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PREFACE

Allergic diseases are very common in the dermatological practice. Skin conditions are one of the most common forms of allergy managed by an allergist making them a major global public health problem. Atopic eczema and urticaria each affect about one in five persons. In five to ten percent of our population, a penicillin allergy is suspected, mostly because of a previous skin rash. Contact dermatitis a leading cause of occupational disease. Urticaria may be the first sign of life-threatening anaphylaxis. Red, bumpy, and itchy skin is irritating, embarrassing and disturbing the sleep due to itch. It leads to a severe reduction of quality of life in affected patients. Our community faces huge direct and indirect costs due to allergic skin diseases by direct health care costs, but also by loss of productivity and absenteeism of patients. Despite increased understanding of the mechanisms leading to skin allergy already have produced advances in treatment options, such as the development of biopharmaceuticals, still a high number of unmet needs remain to be resolved.

To tackle this huge global health problem, the EAACI decided to follow up their highly successful series of allergy atlases with the development of a "Global Atlas of Skin Allergy". With this atlas, EAACI and the editors aim to increase awareness on the global burden created by skin allergies, to provide information on the mechanisms, clinical picture and management of allergic skin diseases, and to reinforce the need for research and interaction in this area and the role of a structured management strategy including education and prevention. It may help to provide information on which structures, existing programs and tools are already in place and guidance on how to overcome remaining barriers in order to progress to novel innovative solutions for the global management.

The "Global Atlas of Skin Allergy" contains 113 chapters written by 118 authors with 92 clinical pictures, 105 illustrations and 70 tables. It covers the basics of skin immunology and mechanisms in the skin, epidemiology, nomenclature, histopathology, skin allergy tests as key elements for allergy diagnosis, the clinical pictures of cutaneous allergic reactions and differential diagnoses, guidance on recognition and management, a comprehensive global assessment of burden as well as strategies for the management allergic skin diseases. It covers common diseases, such as urticaria, angioedema, atopic dermatitis, contact dermatitis, cutaneous drug allerg and mastocytosis. The atlas may serve as an educational tool and desktop reference for medical students, allied health care workers, primary care physicians, pharmacists, medical industry, policy makers, patient organisations and specialists dealing with allergic skin diseases.

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Knut Brockow and Charlotte G. Mortz

Global Atlas of Skin Allergy Editors

FOREWORD

We are well into the era of precision and personalized medicine. Among the challenges is the need to translate information from these efforts into practical aspects of medical care. Application of these initiatives to understanding allergic diseases involving the skin is readily possible due to accessibility of the target organ in question and the continued evolution of techniques that progressively offer more in-depth analysis and insight into all aspects of homeostasis and disease pathology. In this Global Atlas of Skin Allergy, organized and published under the auspices of the European Academy of Allergy and Clinical Immunology, the editors and their international colleagues have undertaken a challenge of significant proportions: to up-date medical care providers, patients and families regarding the latest in the scientific understanding of allergic inflammation of the skin. During my tenure as Chief of the Laboratory of Allergic Diseases and as Chief of the Mast Cell Biology Section within the National Institute of Allergy and Infectious Diseases, I have had the opportunity to meet and interact with a significant number of the authors of this work. They and their dedicated colleagues constitute a wide range of expertise and insight into dermatologic diseases. In this work, their contributions and perspectives are concisely and clearly presented, including within key messages, and with detailed tables and illustrations. The text, tables and figures allow the reader to access and apply relevant information to specific situations. This work will serve the readership well, and appropriately ends with a call to accept allergies as a global health problem, to up-grade "allergy" in the public agenda, and to increase research funding for initiatives in allergology and dermatoallergology.

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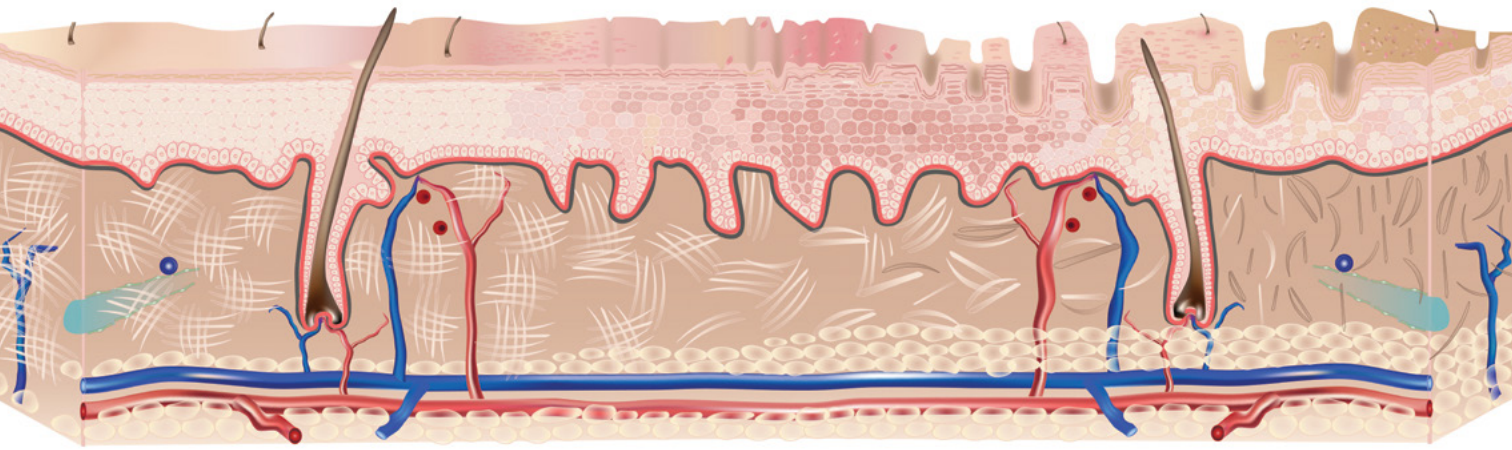

STRUCTURE AND FUNCTION OF THE SKIN

* Function and structure of the skin
* Skin immune system: Mast cells
* Skin immune system:W Langerhans cells
* Skin immune system: Dendritic cells
* Skin immune system: T cells
* Skin immune system: Innate lymphoid cells
* Skin immune system: B cells
* Microbiome of the skin
* Environmental impact on the skin

1 FUNCTION AND STRUCTURE OF THE SKIN

Michael Ardern-Jones
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KEY MESSAGES

- The skin comprises a complex physical structure principally composed of keratinocytes, which demonstrate different biological functions during differentiation and transition from the basal layer to the outermost and ultimately non-viable corneocyte layer
- The skin harbours a complex network of immune cells which carefully regulate the induction of tolerance and immunity
- Breakdown of the skin barrier is central to the induction of inflammatory skin disease including allergy

INTRODUCTION

The skin makes up about 16% of body weight and is one of the largest organs with an average surface area of 1.91 m^2. The biological functions of the skin are numerous, the most important of which is as a barrier to protect the body from noxious external factors and to keep the internal systems intact (Table 1).

Skin is composed of three layers: the epidermis, the dermis and the subcutis (Figure 1). Important derivatives of skin include hair, nails, and glands: sebaceous (sebum production); and sweat (apocrine and eccrine). Additionally, myelinated and non-myelinated nerve fibres are abundant where sensory nerve endings reach the dermis and epidermis via free nerve endings, Merkel cells, and specialist receptors. These signal itch, pain and temperature sensation. Sweat glands, blood vessels, and arrector pili muscles are under autonomic nerve control. Blood and lymphatic vessels are also prominent.

EPIDERMIS

The epidermis is a stratified squamous epithelium comprised of 20-100 keratinocyte cell layers, approximately 0.1 mm thick, although the thickness can be ten times greater on the palms and soles. Keratinocytes produce the protein keratin and are squamous cells functionally similar to all other squamous epithelial cells (e.g. airways and gastrointestinal tract). The epidermal layers reflect different stages of keratinocyte maturation (Figure 2). Melanocytes (located in the basal layer) produce melanin in membrane-bound organelles (melanosomes) which are released into the epidermis and are taken up by surrounding keratinocytes.

DERMIS

The dermis is comprised of a connective tissue matrix of glycosaminoglycans (GAGs), collagen

TABLE 1

Biological functions of the skin		
PROTECTION against	**REGULATION**	**COMMUNICATION**
Trauma	Temperature	Blushing
Dirt/pollution	Vitamin D	Beauty
Infection		Position
Sun damage		Pheromones
Cancer		

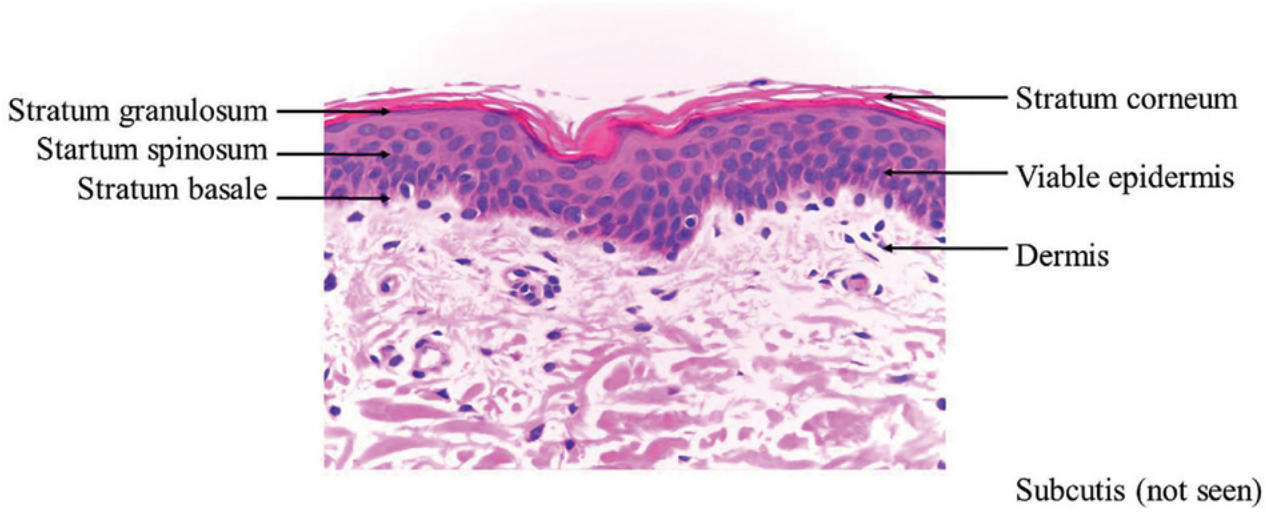

Figure 1 Structure of the skin - The diagram shows the different cellular and compartmental layers of the skin

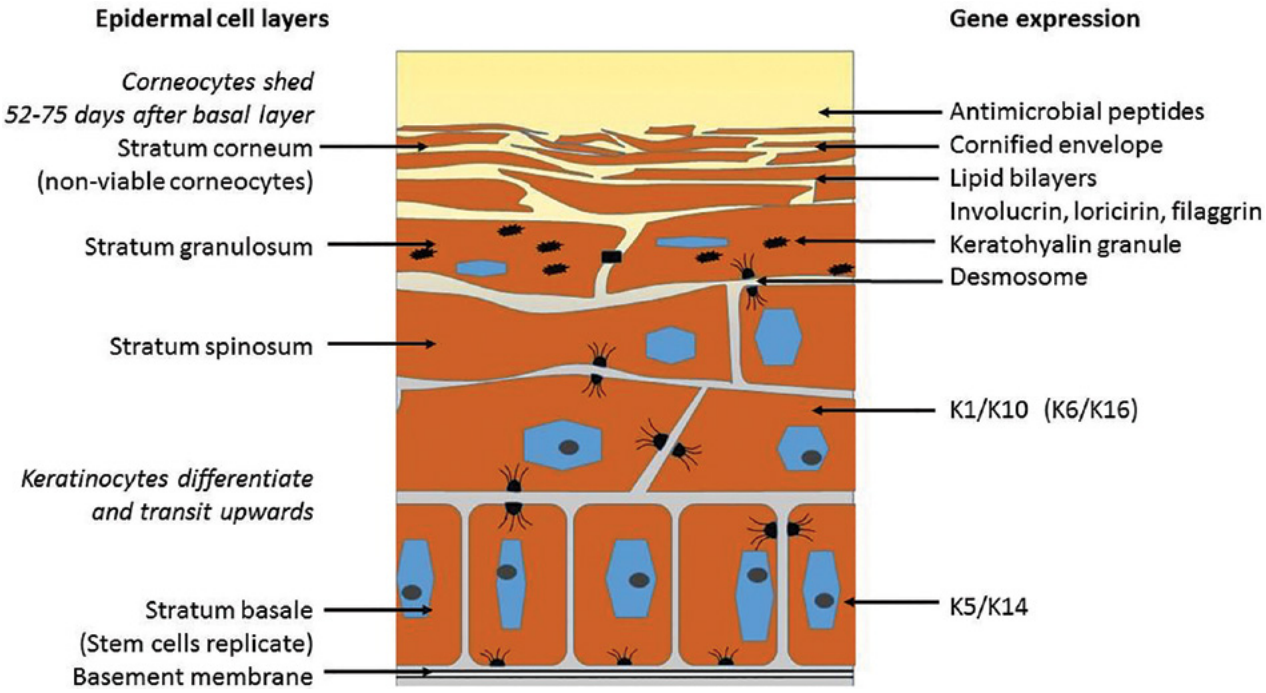

Figure 2 Epidermal layers of the skin and the corresponding gene expression (adapted from (2) (3))

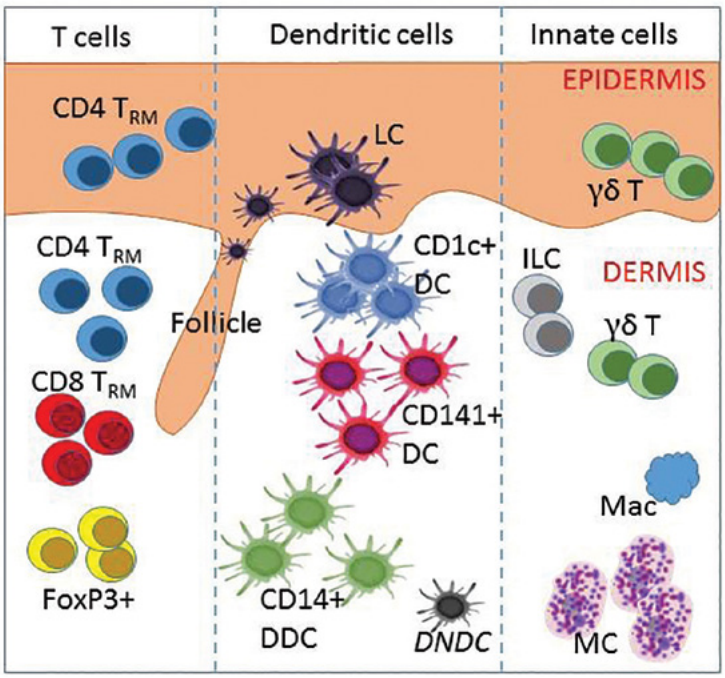

Figure 3 Immune cells in the skin - Resident memory cells provide long lived memory and rapid immunity against pathogens. Dendritic cells, efficiently capture and present antigens to T cells, driving different biological responses. (CD4 T_{RM} - CD4 Resident Memory T cells; CD8 T_{RM} - CD8 Resident Memory T cells; FoxP3+, FoxP3+ CD4+ T regulatory cells (Treg); LC -Langerhans cells. Drive Th17 responses and regulate tolerance; DC - Dendritic cells (CD1c+ / CD141+ / CD14+) drive Th1/Th2 responses; DNDC- Double negative DC (as yet only characterised in mice); ILC - Innate lymphoid cells, release type 2 cytokines on activation; γδ T, γδ T Cells (syn. dendritic epidermal T cells, DETCs); Mac -macrophages; MC - Mast cells (Adapted from (4) (5) (6))

bundles and elastin fibres. Dermal thickness varies in different body sites from 0.6 to 3mm.

SUBCUTANEOUS LAYER

The subcutis (fat, loose connective tissue) is of variable thickness (2-20mm) dependent upon body mass index (BMI), but is fractionally thicker in women compared to men of the same BMI.

THE SKIN IMMUNE SYSTEM

Keratinocytes are highly tuned to sense pathogens through their array of pattern recognition receptors. Signalling induces a rapid inflammatory innate immune signal which initiates host defence and engages other immune cells. The Langerhans cells (epidermis) and dermal dendritic cells are the outermost sentinels of the adaptive immune system and regulate host tolerance or immunity following exposure to exogenous antigens. Application of modern tools to study the immune cell population of the skin has revealed an increasingly complex network of different cells with important roles in antigen presentation (dendritic cells), innate and adaptive immunity (Figure 3). T lymphocytes are both resident (T_{RM}) and circulate through normal skin from the blood. Immunosurveillance is controlled by expression of 'skin homing' molecules, including cutaneous leucocyte antigen (CLA).

Mast cells are principally known for their ability to degranulate and release histamine and other vasoactive molecules. However, mast cells also release a wide range of cytokines, and increasing evidence shows that they have an important role in skin immune responses.

CONCLUSION

The skin has been previously regarded as an inert structure which provides a physical outer 'wrapping' to the human body. However, as outlined above, modern understanding demonstrates the complex interaction between the structural cells and others to tightly regulate critical physiological, biochemical and immunological functions in the skin.

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2a SKIN IMMUNE SYSTEM: MAST CELLS

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KEY MESSAGES

- Human skin mast cells are characterised by the abundant presence of chymase in their granules
- Many peptidergic drugs induce pseudoallergic reactions via activation of chymase-positive mast cell subsets
- The expression of Mas-related G protein-coupled receptors for peptidergic drugs is upregulated in the skin mast cells of patients with chronic urticaria

Mast cells evoke immediate-type allergic reactions through cross-linking of their high-affinity receptors for IgE antibody upon antigen-IgE ligation. These cells induce a similar reaction upon various stimuli in IgE-independent manners, in which most reactions can be mediated by G-protein-coupled receptors (GPRs) such as C5a receptors. Mast cells immediately release chemical mediators such as histamine or tumor-necrotizing factor-α (TNF) stored in their granules when they were activated upon the above stimuli. They also rapidly synthesize and release lipid mediators such as cysteinyl-leukotrienes from arachidonic acid abundantly present in the membrane in a similar time course. Mast cells also synthesise and release various cytokines and chemokines by transcribing the corresponding genes, starting at a few hours after stimulation. Mast cells are also capable of releasing cytokines and chemokines upon stimulation with pathogen-associated molecular patterns (PAMPs) via Toll-like receptors, and upon stimulation with external cytokines, in which the most potent one is IL-33. In these PAMPs- or cytokine-induced activations, degranulation is not normally seen. Using these molecules, mast cells are thought to orchestrate tissue resident immune cell functions and recruitment of additional innate and adaptive effector cells in the earliest event of immunization and allergic inflammation (Figure 1).

Mast cells are known to be heterogeneous depending on the tissue where they dwell, both in humans and in rodents (Table 1). While all human mast cells abundantly express tryptase, human skin mast cells are characterised by the abundant presence of chymase in their granules (mast cells having both tryptase and chymase; MC_{TC}s). On the other hand, lung mast cells or mast cells present in the epithelium almost lack chymase (mast cells having only tryptase; MC_{T}s). The role of these proteases is not fully understood, although they are involved in both physiological and pathological tissue remodeling. MC_{TC}s are activated by opioid molecules via Mas-related G-protein-coupled receptor X2 (MRGPRX2), while MC_{T}s are not activated by them. Meanwhile, MC_{T}s express platelet-activating factor (PAF) receptors and can be activated by PAF, while MC_{TC}s do not. Many peptidergic drugs such as neuromuscular blocking drugs or fluoroquinolone antibiotics induce pseudoallergic reaction via activation of MC_{TC}s present in the skin or cardiovascular system through MRGPRX2 (Figure 2). The expression of MRGPRX2 is upregulated in the skin of patients with chronic urticaria.

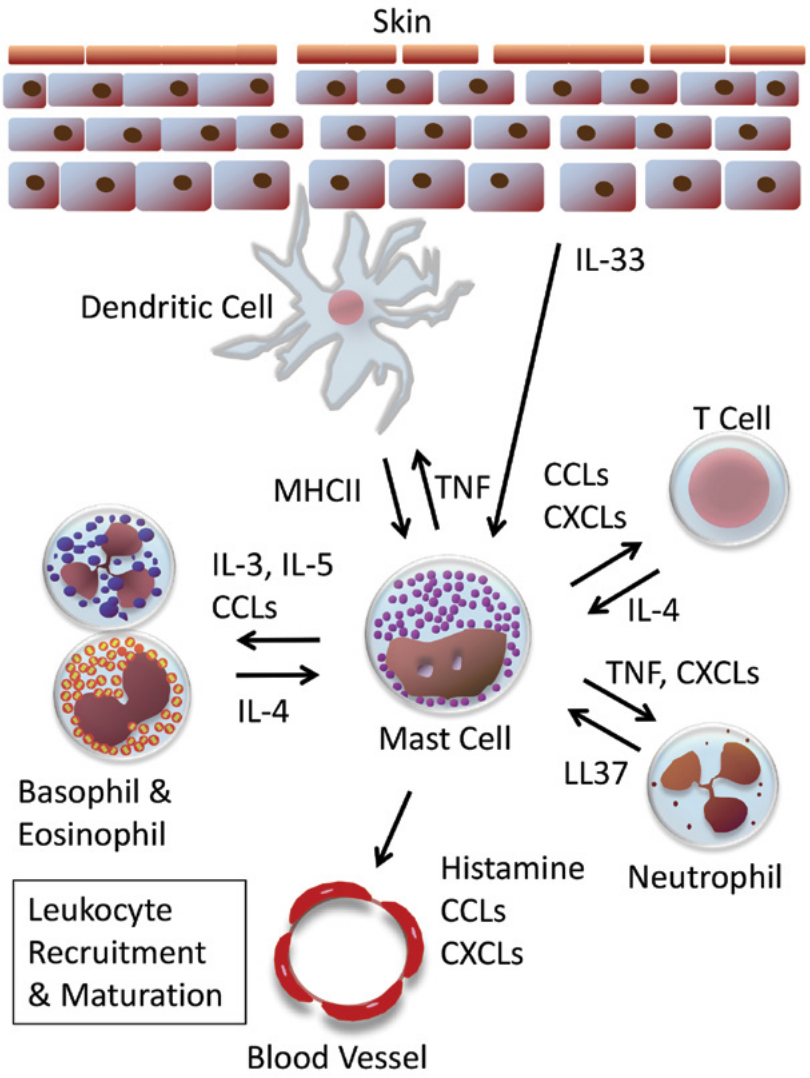

Figure 1 Activation of tissue immune cell functions by skin mast cells. A variety of innate and adaptive effector cells are recruited from skin microvessels when stimulated by mast cell-derived molecules such as TNF and CC-/CXC-chemokines (CCLs/CXCLs). Mutual activation is seen between mast cells and some cell types; i.e., dendritic cells (via TNF and MHC class II molecule, reference #3) and neutrophils (via TNF, CXCLs and a host defensing peptide LL37, reference #2). In addition, cytokines such as IL-4, IL-9 and IL-33 derived from T cells, basophils and tissue resident cells enhance mast cell functions

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TABLE 1

Characteristics of mast cell subsets in mouse and human

Characteristics	Mouse Mast Cells		Human Mast Cells	
	Mucosal Mast Cells	Connective Mast Cells	MC_T	MC_{TC}
Granular Proteases	Mouse Mast Cell Protease-1, -2	Mouse Mast Cell Protease-3, -4, -5, -6, -7	Tryptase	Tryptase Chymase
Distribution	Mucosa	Submucosal tissue	Epithelium, Lung	Connective Tissue, Skin
Granular Proteoglycans	Chondroitin Sulfate PGN-1	Heparin PGN-1	Heparin PGN-2 (Major Basic Protein)	Heparin PGN-2 (Major Basic Protein)
FcεRI-mediated Activation	Yes	Yes	Yes	Yes
Mas-related GPR-mediated Activation	No	Yes (via Mrgprb2)	No	Yes (via MRGPRX2)
Activated by PAF	?	?	Yes	No
Activated by C5a	?	?	Yes	No

Note that definition of human mast cell subsets are different from mouse (rodent) subsets (see reference #1).
MC_T=tryptase-positive mast cells; MC_{TC}=mast cell having both tryptase and chymase

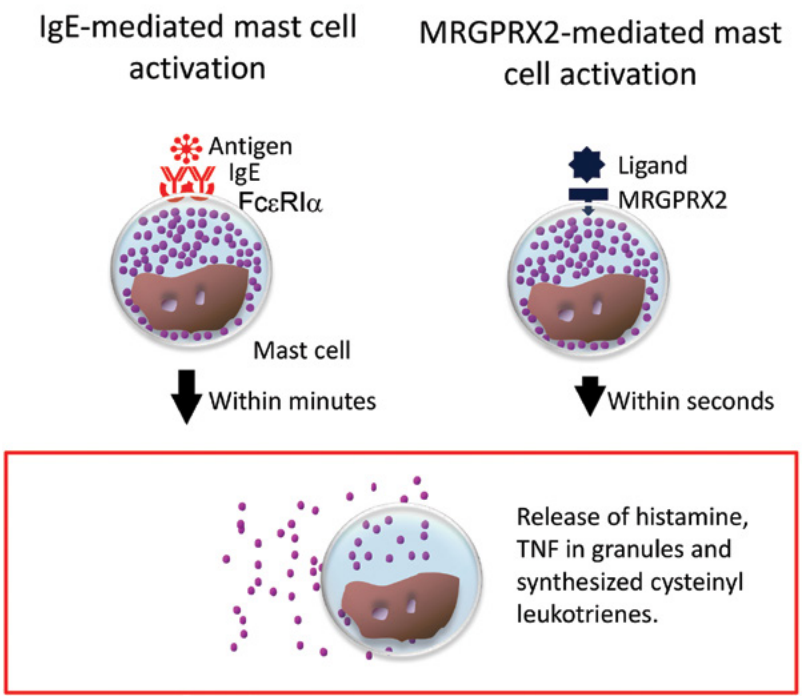

Figure 2 Comparison of IgE- and MRGPRX2-mediated human skin mast cell activation. IgE-mediated mast cell activation occurs when challenged with antigens like food proteins, haptens like antibiotic groups of penicillin/β-lactam, or by autoantibodies against IgE (or FcεRIα). MRGPRX2-mediated mast cell activation was triggered by neuropeptides like substance P, antimicrobial peptides like human β-defensins, host defense peptides like LL37, neuromuscular blocking agents like rocuronium, and fluoroquinolone family of antibiotics like ciprofloxacin (reference #4). Upon activation, in minutes (IgE-mediated) or in seconds (MRGPRX2-mediated), skin mast cells release histamine, TNF and cysteinyl-leukotriens, which are acting on blood vessels, to cause symptoms like urticaria, angioedema, or anaphylaxis

2b SKIN IMMUNE SYSTEM: LANGERHANS CELLS*

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KEY MESSAGES

- Langerhans cells (LC) are members of a group of specialized antigens presenting cells - termed dendritic cells, that can initiate primary immune responses in naive T cells
- LC form a network of antigen presenting cells localized at the interface of the organism and its environment, positioned to sample antigens from epithelial surfaces such as the skin or the airways
- LC initially regarded as the prototype of antigen presenting cells required for induction of T effector cell responses, also play a role in induction of antigen specific tolerance
- Conditions of the cellular microenvironment critically determine the outcome of whether LC prime or induce tolerance

Since their initial description in 1868 by the Paul Langerhans generations of scientists – including many investigative dermatologists - have been intrigued by Langerhans Cells (LC), a small distinct population of cells that reside in the suprabasal layers of mucosal and epidermal epithelia. Due to staining behavior, morphology and proximity to dermal nerve fibers, LC were first considered to be intraepidermal nerve cells. A number of different misconceptions followed, such as LC as worn out melanocytes (effete melanocyte theory), before the concept of LC as immune cells was established in the late 1970s.

LC are now well recognized to be members of a group of highly specialized antigen presenting cells - termed dendritic cells - that are required to initiate primary immune responses in naive T cells. LC form a network of antigen presenting cells that are localized within the epithelial tissues, i.e. at the interface of the organism and its environment (Figure 1 A + B), thus LC are ideally positioned to sample antigens from epithelial surfaces such as the skin or the airways. Due to their unique capacity to migrate to the dermis and the lymph nodes in order to present antigen, LC play a crucial role in immune surveillance and immune homeostasis. Past research efforts have identified critical roles of LC in a vast range of clinical conditions ranging from contact allergy, cutaneous infections, autoimmune disease, HIV and tumor rejection. Concepts of LC cell biology and function, LC ontogeny and lineage, as well as the role of LC in selected disease states has been reviewed extensively. Recent developments of tools that allow the selective and time dependent *in vivo* deletion of LC have accelerated our understanding of various aspects of LC biology under steady state and disease conditions. With each new approach taken we must realize that the function of LC is usually more complex than initially anticipated. It has been recognized for some time that LC are not static, but rather a dynamic group of cells that have the potential to undergo key functional changes at several points during their lifespan. Studies in bone marrow chimeras initially suggested that epidermal LC populations were restored by LC precursors from the circulation. Subsequent experiments in parabiotic mice however have taught us that the restauration is based on skin resident LC precursor cells. Thus un-

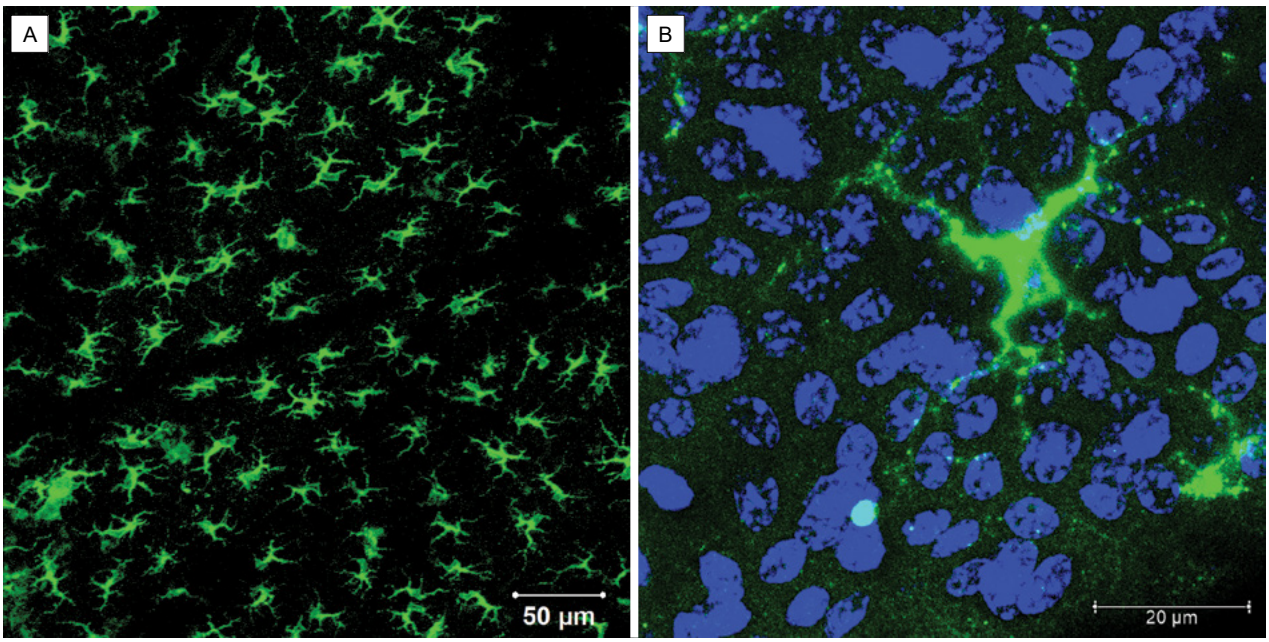

Figure 1 Network of Langerhans cells (green) detected by MHC class II in an epidermal sheet of murine ear skin. A, En face view of an epidermal sheet (overview), B, Langerhans cell (green) with typical dendrites intercalating between surrounding keratinocytes displayed by DAPI staining of cell nuclei

der steady state conditions, adult LCs form a self-renewing population within the epidermis. In contrast rapid loss of LC numbers under inflammatory conditions has been reported to be compensated by replacement of LC derived from monocytic precursors recruited from the circulation. Similarly, LC were initially regarded as the prototype of antigen presenting cell required for induction of T effector cell responses. Over the past years evidence has accumulated that LC also play a role in induction of antigen specific tolerance. Conditions of the cellular microenvironment seem to critically determine the outcome of LC functions. This is best exemplified in a recent study in which inducible expression of neoantigens restricted to LC under steady state conditions led to the development of antigen specific immune tolerance, whereas presentation of the antigen by activated LC resulted in antigen specific memory immune responses. These are just two examples in which the constantly evolving field of LC research has taught us the lesson, that depending on which experimental setting is used and which question is asked the outcomes may seem paradoxical at first sight. Integrating the temporo-spatial relationship, the presence or absence of pathogen or danger associated molecular patterns, the kind of antigen or allergen encountered, and potentially other parameters (e.g. the metabolic condition), is required to understand the full potential of the functional plasticity of this fascinating cell.

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2c

SKIN IMMUNE SYSTEM: DENDRITIC CELLS

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KEY MESSAGES

- Resident in the skin barrier, skin DCs are the most important sensorial immune cells in response to the stimulation of environmental antigens
- Upon stimulation, activated skin DCs migrate to lymphoid organs where they initiate antigen-specific Th responses. Pro-inflammatory or tolerogenic functions mediated by skin DCs play essential roles in both healthy and diseased skin
- Multiple types of skin DCs form a skin DC network, in which skin DCs co-operate with each other to mediate their functions
- The local skin microenvironment influences the functions of skin DCs. The pro-inflammatory and chemotactic mediators released by themselves as well as other skin immune cells profoundly affect skin DC functions

The skin represents an effective physical, microbial, and immunological barrier that protects the human body from environmental hazards. The skin senses and responds to invading allergens and pathogens due to the existence of a sophisticated network of skin dendritic cells (DCs) (Figure 1). Skin DCs recognize, capture, and process invading environmental antigens. Upon antigen stimulation, skin DCs become activated and migrate into lymph nodes (LNs) where they provide antigen peptides, co-stimulatory as well as cytokine factors to naive T cells and thereby initiate antigen-specific humoral and cellular immune responses. The type, migration and activation stage of skin DCs are essential for both healthy and diseased skin. Multiple types of DCs are involved in the regulation of skin immunity by mediating either skin tolerance or inflammation. Two types of DCs, known as myeloid DCs (mDCs) and plasmacytoid DCs (pDCs), express the high-affinity IgE receptor (FcεRI). Endowed with significant type I interferon (IFN) production, pDCs not only protect skin from viral or bacterial infection but mediate autoimmune responses. Beside cytokine secretion, pDCs promote naive T cells differentiation into Th17 cells which are essential for tissue defense and skin inflammation. Furthermore, TLR-activated human pDCs induce the expression of SOCS1 and SOCS3, which actively suppress type I IFN production through the mechanism that SOCS1- and SOCS3-bind IFN regulatory factor 7 to promote its proteasomal degradation. As compared to pDCs, mDCs are more often observed in human skin and exert tolerogenic or proinflammatory functions. The cytokine and chemokine milieu in the skin influences the function of skin DCs during either the initiation stage or active phase of skin diseases. Upon allergen stimulation, skin epithelial cells release tissue cytokines, such as IL-33 and thymic stromal lymphopoietin (TLSP), which activate skin DCs and promote specific-IgE production and Th2 responses. Inflammatory skin from allergic patients, such as patients with atopic dermatitis (AD), contains high numbers of resident and skin infiltrating DCs, such as Langerhans cells (LCs) and inflammatory epidermal dendritic cells (IDECs). Although the origin of LCs in the steady-state and inflammatory human skin is under debate, LCs are the most prominent skin DCs and exist in both healthy and

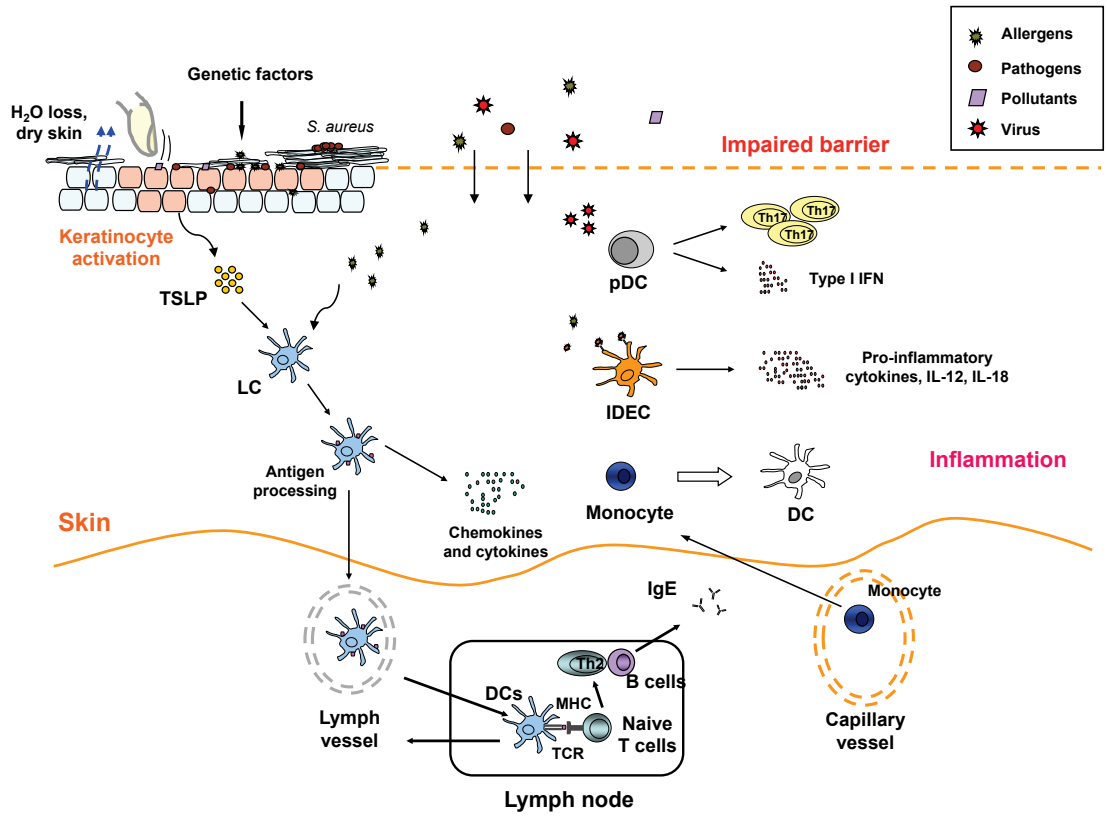

Figure 1 Atlas of human skin dendritic cells

inflammatory skin. LCs capture allergens and present those antigens to T cells to trigger Th2 responses. Furthermore, allergen stimulation of skin epithelial cells as well as FcεRI crosslinking on LCs by allergen-bound specific IgE leads to the release of different cytokines and chemokines which recruit other skin immune cells including IDECs. Because IDECs are only present at inflammatory epidermal sites and release a high amount of pro-inflammatory mediators after IgE-receptor mediated allergen challenge, IDECs are the major skin DCs which amplify the epidermal inflammatory reactions in allergic patients. Monocytes can differentiate into DCs under inflammatory milieu and thereby contribute to the homeostasis of the skin. Attenuated IFN-γ and TGF-β signaling and responsiveness of monocytes from patients with atopic dermatitis might promote Th2 responses due to decreased TGF-β signaling on one side and impaired Th1 cytokine IFN-γ stimulation on the other side. Together, the recruitment and differentiation of DCs from their precursors, activation and interactions of various types of skin DCs form a complicated network which shapes the outcome of skin immunity.

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2d SKIN IMMUNE SYSTEM: T CELLS

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KEY MESSAGES

- Atopic Dermatitis (AD) is a systemic type 2 immune response-driven disease rather than inflammation limited to skin
- Allergic contact dermatitis has been observed in approximately 20% of the general population to common haptens such as fragrances, preservatives, and metals in which a T cell response to responsible low-molecular weight chemicals have been demonstrated
- The activation and skin migration of particularly skin-homing T cells is a key pathogenetic mechanism in atopic dermatitis, allergic contact dermatitis and T cell-mediated drug exanthems
- Endotypes of AD have been proposed, such as type 2 AD, non–type 2 AD with a combination of T_H1-, T_H17-, and T_H22-driven inflammation as well as epithelial dysfunction
- IL-33, IL-25 and TSLP directly or indirectly induce the development of type 2 response in the skin
- Non–type 2 immune response AD (intrinsic AD) demonstrates a combination of T_h1-, T_h17-, and T_h22-driven inflammation
- MAIT cells have been recently described that are anti-bacterial and anti-fungi invariant T cells responding to riboflavin and utilizing MR1-MHC molecules

Activation and skin migration of immune cells play an essential role in the pathogenesis of several allergic skin diseases such as atopic dermatitis (AD), allergic contact dermatitis (ACD) and drug exanthemas. A wide variety of T cells infiltrate the skin and play roles in various skin inflammatory diseases (Table 1). Resident memory T cells (T_{RM}) are non-recirculating memory T cells that persist long-term in the skin as well as all mucosal tissues. T_{RM} are characterized with a fundamentally distinct gene expression program that differentiates them from circulating T cells. They first encounter a pathogen and afterwards do not leave the skin. Allergens, tissue injury and autoantigens activate T_{RM} in diseases such as AD and fixed drug eruptions. These cells play a protective role against infectious agents.

AD is associated with other atopic diseases, such as allergic rhinoconjunctivitis, asthma and food allergy, and represents a systemic type 2 immune response-driven disease rather than inflammation limited to the skin. A hallmark cellular composition of atopic dermatitis is the marked influx of T cells in both dermis and in the epidermis of the lesional AD skin (Figure 1). In non-lesional skin of atopic dermatitis patients, T cells are moderately increased in the dermis. Allergen-specific T cells particularly infiltrate the AD skin. In addition, auto antigen- and microbial antigen-specific T cells have been identified. Further coining the role of T cells in the pathogenesis, different endotypes of AD have been proposed, such as type 2 immune response AD, non–type 2 immune response AD with a combination of Th1-, Th17-, and Th22-driven inflammation as well as epithelial dysfunction.

The elicitation of ACD or contact hypersensitivity starts with the sensitization and clonal expansion of contact allergen-specific T cells (Figure 2). Skin infiltration

TABLE 1

T cell subsets in the skin. Different conventional and non conventional T cells and their major functions are shown	
CD4 TH1	AD chronic lesions, ACD, drug exanthemas, mechanisms of eczema formation
CD4 TH2	AD lesions, AD and general allergy allergen-specific Th2, eosinophilic skin disease
CD4 TH17	AD chronic lesions, psoriasis, neutrophilic drug exanthemas
CD4 TH22	AD late lesions
CD4 Treg	Controls overactivation of other subsets in peripheral blood and lymphatic organs in AD, ACD. Does not exist too many in lesional skin
T_{RM}	Resident memory T cells, mainly against infectious agents, mostly CD8
gd T cells	Against infectious agents in mice, very few in human skin
CD8 TH1	Against viruses and other infectious agents, found in AD and ACD skin and drug exanthemas
CD8 TH2	AD, eosinophilic skin diseases
MAIT cells	Mucosal-associated invariant T cells, against bacteria and fungi, riboflavin responsive and MR-1 tetramer responsive

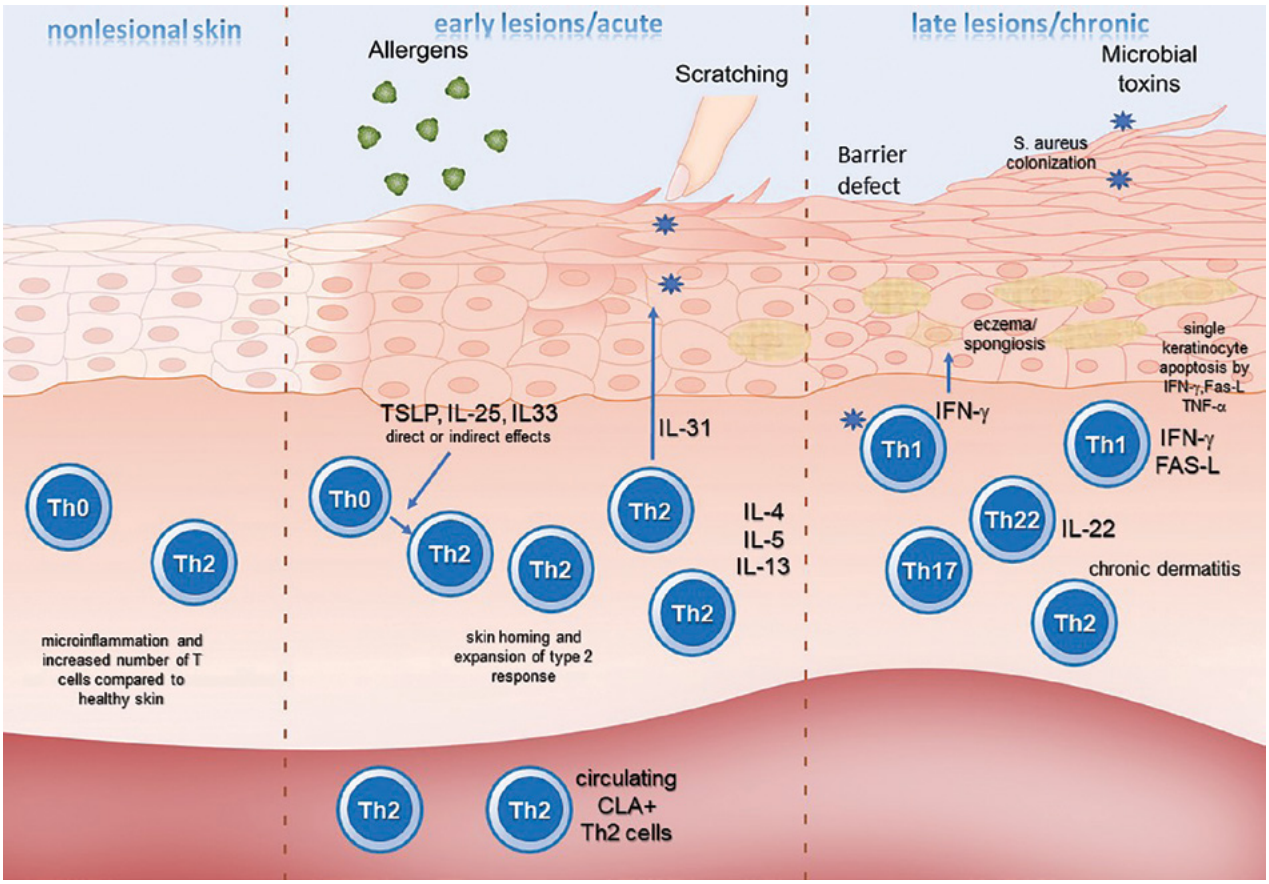

Figure 1 T cells in atopic dermatitis. T cells in uninvolved skin, early lesions and chronic lesions of type 2 AD. T cells are moderately increased in the dermis in the dermis of non-lesional skin. Skin homing CLA+ T cells display a Th2 profile in early lesions and in the circulation. However, in the course of the disease, increasing populations of Th1 cells and IFN-γ and sometimes Th17 and Th22 cells are detected in chronic lesions of AD. IL-33, IL-25 and TSLP released from keratinocytes directly or indirectly support the type 2 response. IL31 released from T cells plays a major role in itch

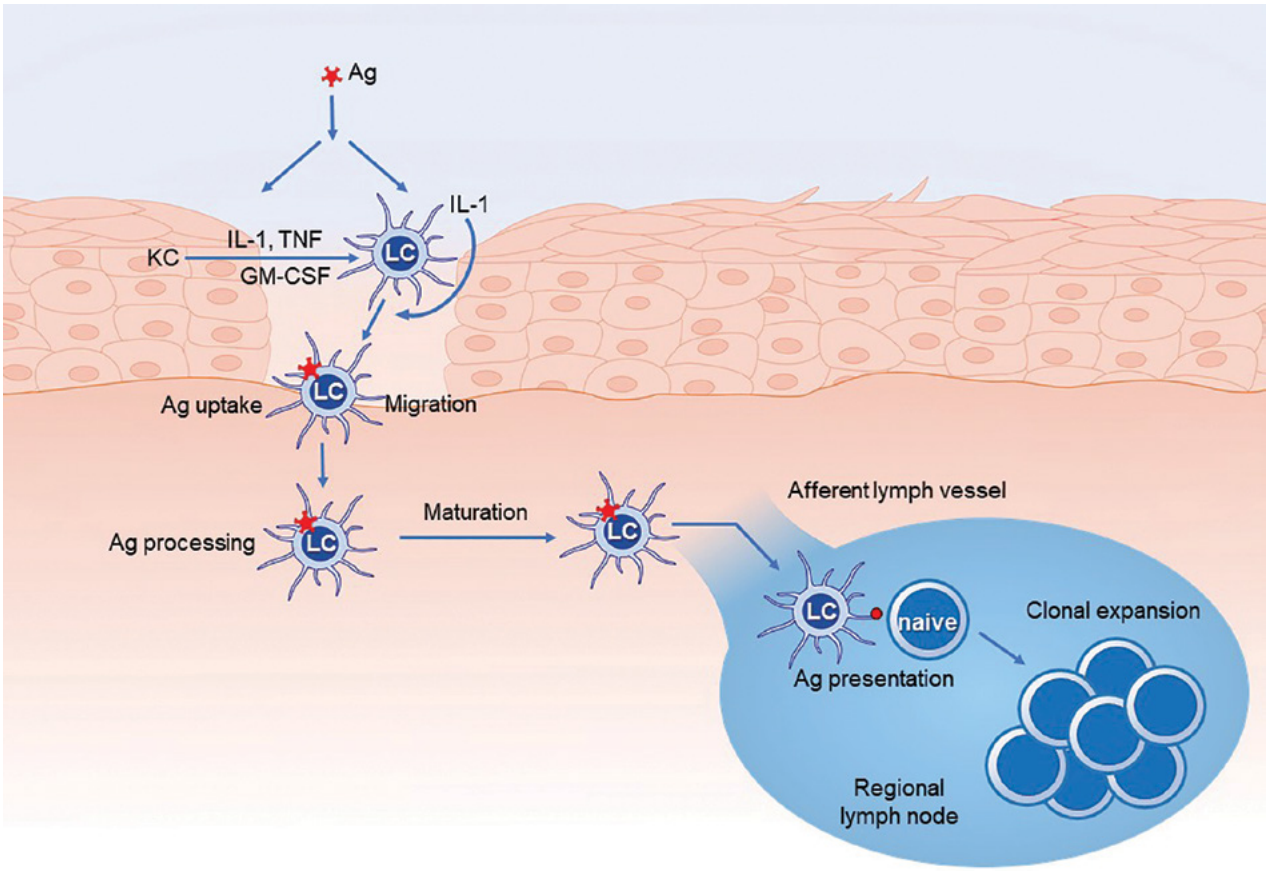

Figure 2 T cells and sensitization against contact allergens in allergic contact dermatitis. Contact allergen is taken up by Langerhans cells that migrate to regional lymph node and activate and proliferate naive T cells. Naive T cells go back to skin and cause eczema in the skin upon reexposure to contact allergen

of CD4 and CD8 T cells and clusters of these cells with dendritic cells is characterized with a type 1 immune response with IFN-γ, the main effector cytokine. Contact allergen is carried to the regional lymph node by langerhans cells and there stimulates the T cells. Activated and clonally expanded T cells go to skin and cause ACD lesions, which usually form an eczema induced by Th1 cells and their cytokine IFN-γ, Fas-Fas-ligand interaction.

In drug hypersensitivity reactions, allergic-immune mechanisms develop against the neo antigens that are formed by drugs or chemicals covalently bound drugs to proteins. IgE development utilizes a T cell response to new antigens in the development of specific IgE. The p-i ("pharmacological interaction with immune receptor") concept represents an off-target activity of drugs with immune receptors (HLA or TCR), which can result in stimulations of T cells.

Mucosal-associated invariant T (MAIT) cells represent a novel subpopulation of innate-like T cells that with an invariant T cell receptor (TCR) α chain and not restricted TCRβ chains. They recognize a distinct set of small molecules, vitamin B metabolites (riboflavin), which are driven from some bacteria and fungi and respond to these molecules in the context of an evolutionarily conserved major histocompatibility complex-related molecule 1. MAIT cells may play unique and important roles in host immunity against pathogens. Their role in AD, ACD, psoriasis and drug eruptions is not known so far.

In AD, circulating skin homing T cells display a Th2 profile followed by early infiltration of skin by Th2 cells. However, in the course of the disease, increasing populations of Th1 cells and IFN-γ are detected in chronic lesions of AD. T cells cause keratinocyte apoptosis and spongiosis in the epidermis between stratum corneum and stratum basale as a key mechanism of eczema development (Figure 1). IFN-γ, Fas-ligand, TNF-α are ma-

jor players in skin keratinocyte apoptosis. Recently, Th17 and Th22 polarizations have been described in addition to Th2 polarization in AD. In addition to CD4 T cells, CD8 T cells are found in AD skin that are potent secreters of IFN-γ, IL-13 and IL-22 and are suggested to be relevant for the early responses in AD.

The high proportion of systemic Th2-polarized T cells secreting IL-4 and IL-13 appears to be a key factor in AD, since pharmacological inhibition of the common receptor the IL-4R-α by dupilumab is rapidly improving the course of the disease. A relatively high number of studies are currently ongoing with other specific antagonists against the cytokines and cytokine receptors. Several Th2-associated serum biomarkers, such as CCL17, TARC, MDC, eotaxin, IL-31, and ECP correlate with the disease severity and therapeutic response of AD.

One of the main reasons for systemic type 2 response is that a big area of epidermal keratinocytes is the major source of IL-33, IL-25 and TSLP in the skin. These cytokines induce the type 2 response directly on T cells and ILC (IL-25), mostly through ILCs (IL-33) and mostly through dendritic cells (TSLP). Another T cell cytokine IL-31, a major factor for pruritis is primarily produced by Th2 cells. It signals through the IL-31 receptor (IL-31R), which is expressed on keratinocytes and nerve fibers (Figure 1). Targeting IL-31 is an efficient treatment of pruritis. Furthermore, IL-31 serum levels correlate with AD severity and itch sensation in cutaneous T cell lymphoma patients. However, as IL-31 induces a delayed onset of pruritus, it may actually be caused by an indirect mechanism.

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2e SKIN IMMUNE SYSTEM: INNATE LYMPHOID CELLS

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KEY MESSAGES

- Innate lymphoid cells (ILCs) are divided into 3 different subsets, similar to the helper T-cell subsets, i.e., Th1, Th2 and Th17 cells
- Group 2 ILCs (ILC2s) are known to be involved in the pathophysiology of atopic dermatitis through their type-2 cytokine production
- Cytokines produced by epithelial cells and basophils, and prostaglandin D2 (PGD2) produced by mast cells, may be crucial for migration and activation of ILC2s
- ILC2s are also involved in skin tissue repair
- E-cadherin, expressed on keratinocytes in healthy skin, suppresses ILC2s through interaction with KLRG-1

Since the skin is the outermost layer of the human body and is always exposed to the external environment, it must form a tight barrier to protect against foreign substances and invaders. Innate lymphoid cells (ILCs) are relatively newly identified immune cells that have no antigen receptors, but they have a lymphoid morphology and are thus thought to be a type of innate immune cell. ILCs are divided into 3 different subsets, similar to the helper T-cell subsets (Figure 1). Of these, group 2 ILCs (ILC2s) are known to be involved in skin allergic diseases and tissue repair.

Skin ILC2s that express killer cell lectin-like receptor G1 (KLRG1) are suppressed by a KLRG1 ligand, a cell adhesion molecule–E-cadherin–that is expressed on keratinocytes in heathy skin. However, once E-cadherin is downregulated due to disruption of the skin barrier, as seen in patients with atopic dermatitis (AD), inhibition ILC2s is abrogated that results in activation of ILC2s. Such ILC2s exhibit an activated phenotype, i.e., higher expression of cytokine receptors for such epithelial-derived cytokines as IL-33, TSLP and IL-25, in the lesional skin of AD patients compared to healthy skin. In line with this, a study using an animal model showed that IL-33, IL-25 and/or TSLP are involved in development of AD-like skin lesions through production of type-2 cytokines by ILC2s, even in the absence of acquired immunity (Figure 2). Those findings suggest that an epithelial-derived cytokine–ILC2 axis may be crucial for development of AD.

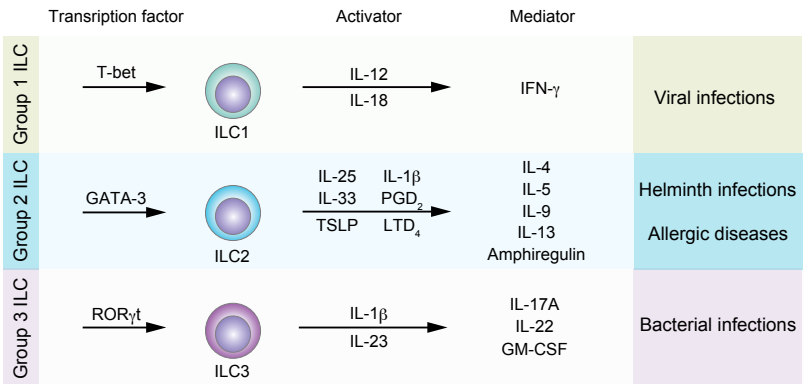

Figure 1 Classification of innate lymphoid cells

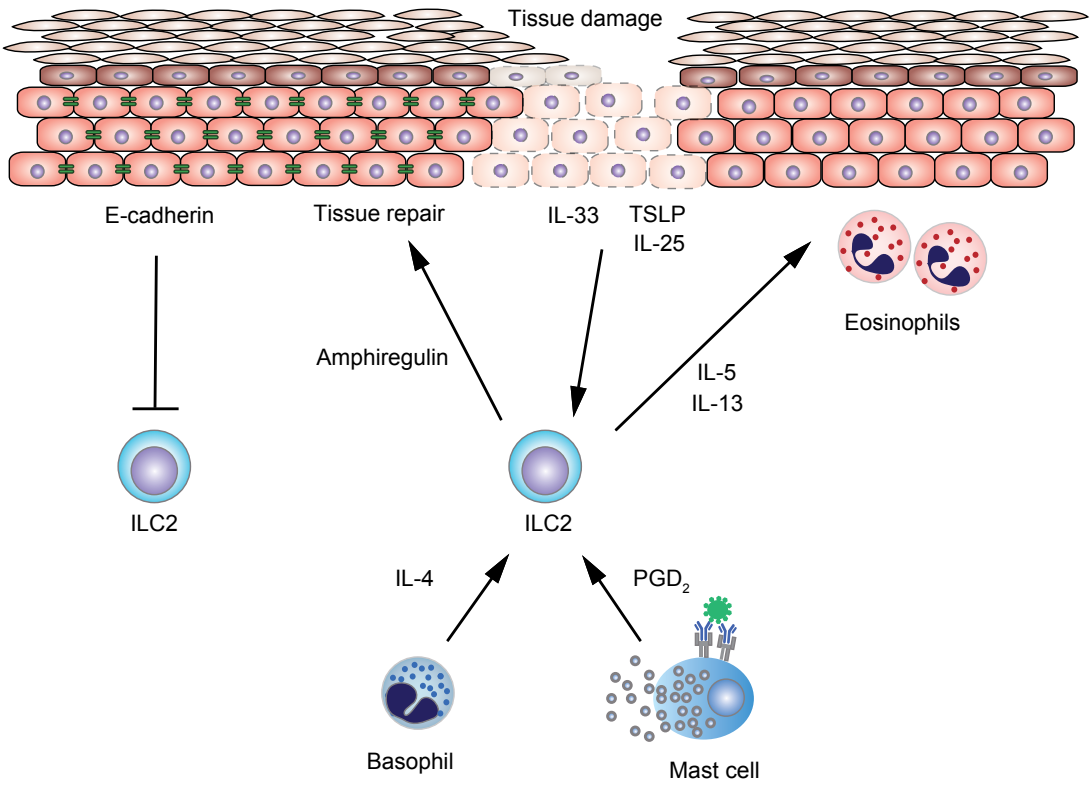

Figure 2 Roles of ILC2 in skin

In addition to interacting with epithelial cells, ILC2s also interact with other immune cells to form an immunological barrier. ILC2s are located in close proximity to basophils in the papillary dermis of lesional skin of AD patients. In line with that, in a mouse model, basophil-derived IL-4 was shown to be crucial for activation of ILC2s and development of AD-like skin lesions. Prostaglandin D2 (PGD2) that is produced mainly by mast cells, is known to induce migration and activation of ILC2s from human skin, also suggesting possible interaction between mast cells and ILC2s (Figure 2).

Skin ILC2s are also involved in tissue repair. In humans, skin-resident ILC2s expressed amphiregulin, a member of the epidermal growth factor family, at a significantly higher level compared to peripheral-blood ILC2s. In addition, ILC2s were seen to accumulate in the papillary dermis and granulation tissue 10 days after wounding. In line with that, in a mouse model, cutaneous wound healing was delayed in the absence of IL-33 and ILC2s, suggesting that an IL-33–ILC2 axis is crucial to tissue repair (Figure 2).

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2f

SKIN IMMUNE SYSTEM: B CELLS

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KEY MESSAGES

- Activated circulating B cells in peripheral blood of AD patients and hyper IgE is observed in extrinsic AD patients
- B cells are not predominant but relatively rare not only in homeostatic conditions, but also in lesional biopsies of inflammatory skin conditions, such as AD
- B cells undergo maturation to plasma cells, production of immunoglobulins and class-switching in response to antigen exposure and T-cell help or similar
- Pan B cell depletion with rituximab is beneficial in AD
- Epicutaneous sensitization for IgE and IgG production is an important aspect in AD

The skin is one of the largest organs in the human body with an active surveillance and residency of immune system cells. It is anatomically composed of two layers. The epidermis is having epithelial cells known as keratinocytes, Langerhans cells, and CD8+ cytotoxic T cells. The dermis consists of diverse immune cells including antigen-presenting dermal dendritic cells, T cells, B cells, and natural killer cells, together with mast cells, monocytes, and macrophages. In recent years our understanding of the functions of skin-resident immune cells have been increased significantly. Studies indicate that B cells are infrequently found in normal skin under homeostatic conditions, and because of their insufficient number has made it difficult to phenotype and quantify them. It is currently unknown whether these cells represent a specific skin-resident population or whether they are derived from circulating populations of B cells. Factors governing the maintenance of B cell populations within the skin have yet to be investigated, as well as the mechanisms governing B cell circulation through the skin. It is also not well studied whether B cells express chemokine receptors for trafficking to skin similar to T cells. Further analysis of B lymphocyte populations present in normal skin will be necessary to understand possible contributions of B cells to skin homeostasis and immuno-surveillance (Figure 1).

In humans, dermal B cell infiltrates have been observed in chronic inflammatory skin conditions including cutaneous leishmaniasis, diffuse cutaneous sclerosis, and atopic dermatitis (AD). B cells appear to contribute to cutaneous inflammation via interactions with both innate immune cells and T cells. B cells undergo maturation and class-switching in response to antigen exposure and T-cell help. Extrinsic type of AD has a hallmark of hyper IgE and increased multiple allergen-specific IgEs against allergens, suggesting an important role of B cells in AD. So far, early B-cell differentiation has not been defined in patients with early-onset AD. Peripheral B and T cells are altered, but T cells predominate in skin lesions in pediatric patients with early AD. IgG1+ B-cell immunity against food allergens in epicutaneous sensitization precedes the generation of IgE responses. Therefore, the assessment of allergen-specific cellular and humoral IgG1+ immunity may help to identify individuals at risk of developing IgE-mediated food allergy.

It is presently unclear as to why B cell depletion in the context of

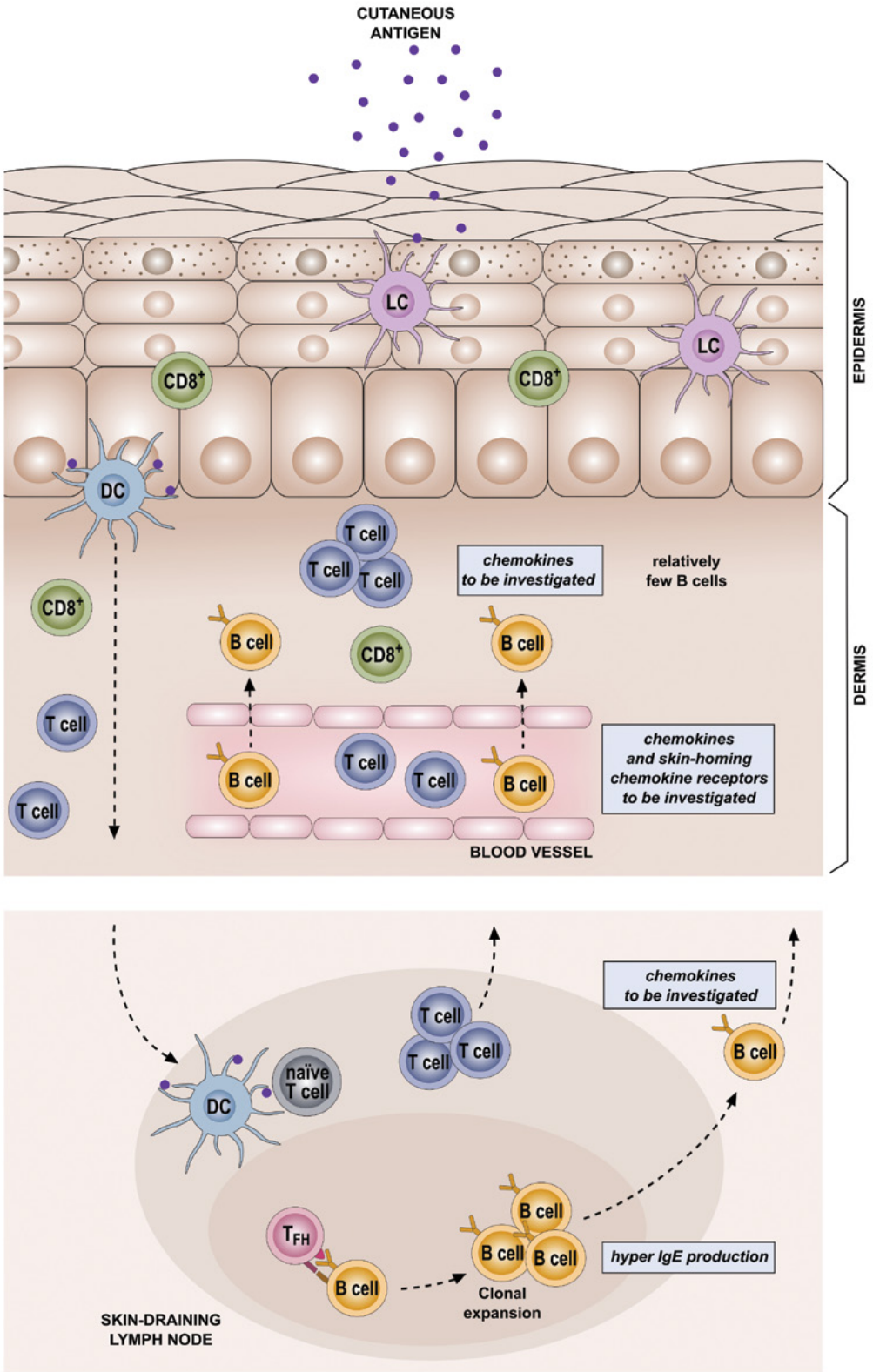

Figure 1 Role of B cells in skin. There is relatively few B cells in the lesional skin of AD. There is not much known about their skin homing chemokines and chemokine receptors in human. Hyper IgE production is a hallmark of extrinsic type of AD

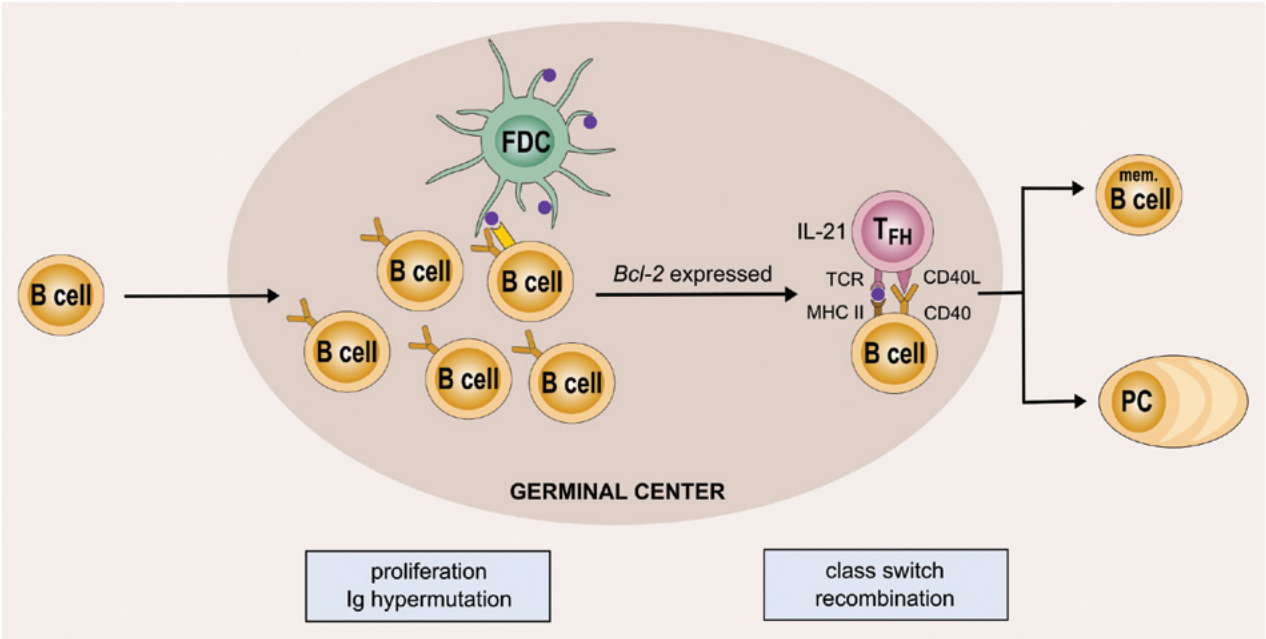

Figure 2 B cell development in germinal center. A B cell enters a germinal center and undergoes proliferation and hypermutation of its immunoglobulin genes. Antigen is presented by the follicular dendritic cell only Bcl-2- expressing B cells escape from apoptosis. Interaction with T follicular cells and T cells promotes class switching. B cells leave the germinal center to become either plasma cells or B memory cells

certain forms of skin inflammation such as AD or immunobullous disease is beneficial in reducing inflammation, whereas in other settings it conversely induces an inflammatory response such as in psoriasis. CD20+ B cells encompass both effector and regulatory B cell subtypes, and therefore Rituximab could, in theory, deplete both pro- and anti-inflammatory subsets of B cells. The apparently conflicting observations in human skin inflammation may be the result of different contributions of effector and suppressor B cells to the pathogenesis of specific diseases.

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3 MICROBIOME OF THE SKIN

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KEY MESSAGES

- A diverse microbiome is present on healthy skin
- AD is associated with higher levels of *S. aureus*
- Targeting the skin microbiome may be included in future therapeutic approaches to managing skin inflammation

The skin is home to a diverse milieu of bacteria, fungi, viruses, bacteriophages and archaeal communities. The skin microbiome, defined as the sum of these microbes, their genomic elements and interactions in a given ecological skin niche, is influenced by age, gender, ethnicity, climate, UV exposure and lifestyle factors. The development and application of culture independent approaches (such as metagenome shotgun sequencing) have revolutionized the characterization of the skin microbiome and have revealed a previously under-appreciated phylogenetic and functional granularity of skin-associated microbes in both health and disease states. The physiology of a given skin niche drives the site-specific differences in bacterial phyla composition of healthy skin. *Propionibacterium* species are commonly found on sebaceous sites, while *Corynebacterium* and *Staphylococcus* species thrive in moist microenvironments. Within the skin mycobiome, *Malassezia* species represent the most predominant fungal flora on the human bodies. Little is currently known concerning the spectrum of viral and bacteriophage communities present on the skin or their interactions with the microbiome and host cells, but may be of significant relevance to conditions such as eczema herpeticum.

The continuous molecular cross-talk between cutaneous epithelia, tissue resident innate and adaptive immune cells and skin-associated microbes allows the establishment of commensal organisms, which have essential roles in protection from invasive pathogens, educating the host immune system and the breakdown of skin-derived lipids and metabolites. Interactions between skin microorganisms may be synergistic or competitive.

Changes in the skin microbiome have consistently been associated with atopic dermatitis (AD). In particular, *Staphylococcus aureus* overgrowth with concomitant decline in *S. epidermidis* is a general feature associated with AD and is not restricted to eczematous lesions. *S. aureus* colonization is evident in 90% of AD cases, associates with AD severity and increased allergen sensitization. AD associated changes in skin biology facilitate S. aureus overgrowth, while *S. aureus* proteases and toxins may further damage the skin barrier and promote local inflammatory responses (Figure 1). Intervention studies with antimicrobials targeting *S. aureus* can reduce AD severity. Restoration of the epithelial barrier with anti-inflammatory and emollient use may also increase microbial diversity of lesional skin. Importantly, direct manipulation of the skin microbiome may offer novel therapeutic opportunities, as has been seen with the emollients supplemented with bacterial lysates, or with topical administration of *Rosemonas mucosa*, *S. hominis* or *S. epidermidis*. These approaches may help correct the imbalance in skin-associated microbial community structures, thereby controlling *S. aureus* overgrowth.

The human skin microbiome is abundant in bacteria, fungi and

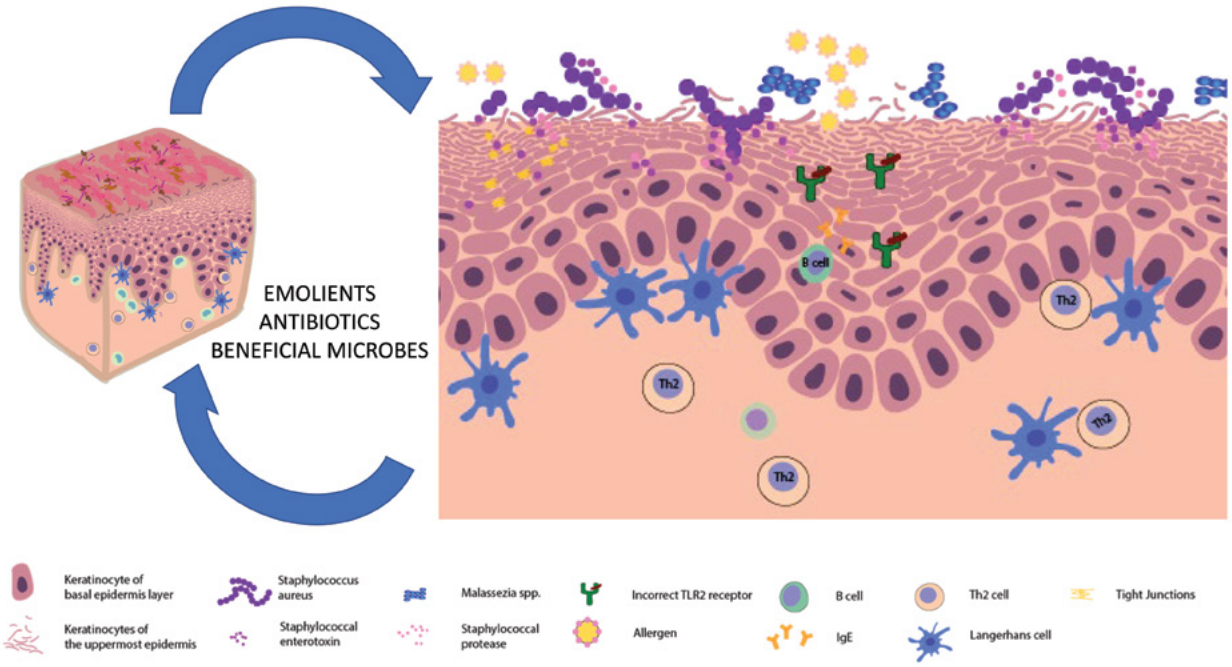

Figure 1 Microbiome of the skin

other microbes, and certain communities preferentially colonize specific niches. Atopic dermatitis skin creates such a specific niche itself. Key pathophysiological features of atopic dermatitis skin are: altered composition of lipid barrier and epidermal barrier dysfunction, downregulation of keratinocyte differentiation markers (ex. filaggrin), defective Toll-like receptor 2 (TLR2) expression on Langerhans cells, increased uptake of potentially allergenic antigens, subsequent lymphocyte priming and infiltration with immune cells characteristic for Th2 type of inflammation. These features associated with atopic dermatitis skin are conductive to colonization by *Staphylococcus aureus*. Atopic dermatitis skin is also more abundant in *Malassezia* species. Colonization by *S. aureus* and *Malassezia* species is associated with disease severity, however it is not limited only to lesional skin. Staphylococcal proteases directly and indirectly (through activation of protease-activated receptors (PARs) on epidermal cells) contribute to the disruption of epidermal barrier. Staphylococcal enterotoxins further disrupt epidermal integrity and act as allergens. Staphylococcal exotoxins damage keratinocytes and activate mast cells. Mast cell products further contribute to cutaneous inflammation. This pathogenic positive feedback loop can be interrupted by the use of emollients, topical antibiotics or topical beneficial microbes.

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4 ENVIRONMENTAL IMPACT ON THE SKIN

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KEY MESSAGES

- Skin barrier homeostasis is influenced by environmental impact – depending on the individual genetic susceptibility and microbiome
- The skin is endowed with versatile methods of defence against environmental hazards
- Pollutants can reach both superficial and deeper skin layers by transcutaneous and systemic routes
- Further research is needed to understand the molecular mechanisms of the environment – skin interaction

Our skin forms a tight barrier to the outside world and as such it is a first point of contact from a host of environmental influences such as pollution, allergens, radiation and pathogens (Figure 1). The interplay between the environment and skin is complex. It is influenced by not only the environmental factors themselves but also the host's genetic susceptibility and the (skin) microbiome. Notably, the skin is endowed with versatile methods of defence against hazards such as penetration, fluid loss from the body, thermal stress, solar radiation, physical trauma and microbial agents. Diseases that can develop due to environmental stresses are e.g. eczema, contact dermatitis, halogen acne, chemical (de)pigmentation, connective tissue diseases and skin cancer.

Allergies are an environmental disease which can arise due to a specific genetic background and where the environment can be defined as the sum of exposure to physical, biological, and psychosocial factors. Hypothesis claims that skin barrier dysfunction is the first step for the penetration of allergens and trigger factors and thus the beginning of the atopic march, i.e. the natural progression of allergic disease. Certain allergens such as pollen have been shown to directly influence the immunological barrier of the skin and pollution itself can increase the susceptibility towards allergies, making anthropogenic factors an important issue for allergies as well.

Pollution is not only important in the severity of allergic symptoms but has also been linked to skin ageing, wrinkle formation and skin spot pigmentation which are additional factors for skin damage on top of the well recorded damage by UV radiation (Figure 1). Pollutants can reach both superficial and deeper skin layers by transcutaneous and systemic routes. As skin is one of the main targets of pollutants and as air pollution is controllable many of these adverse health effects could be prevented.

Human skin is, however, as a healthy barrier also dependant on its microbiome which plays an important role in either impairing or enhancing skin health and a shift in these bacterial communities can even contribute to a disease. Skin disorders which arise partially due to an imbalance of the healthy skin microbiota include atopic dermatitis, acne, seborrheic dermatitis and chronic wounds.

Further research will be necessary to build on our understanding of the complex interplay between skin and the environment, especially with regard to climate change and our modern lifestyle

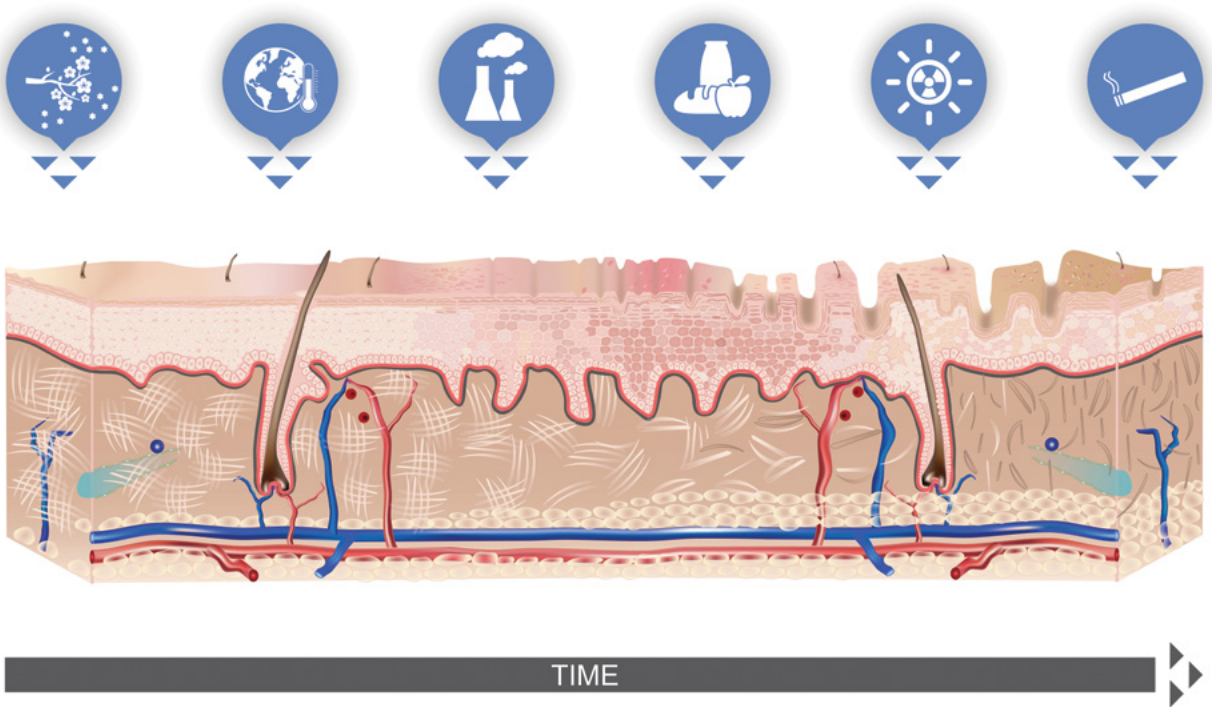

Figure 1 Over the life span the skin is influenced by multiple environmental effects. Depending on the individual genetic susceptibility skin homeostasis can be disturbed by the environment. The sequelae of environmentally induced harm on the skin are multiple and diverse ranging from barrier disruption and sensitive skin, development of atopic eczema and allergies up to the induction skin cancer. Understanding the molecular mechanisms of skin-environment interaction will open new avenues in protective measures towards environmental harm and prevention of environmentally triggered diseases such as allergies

and the additional challenges this brings to health.

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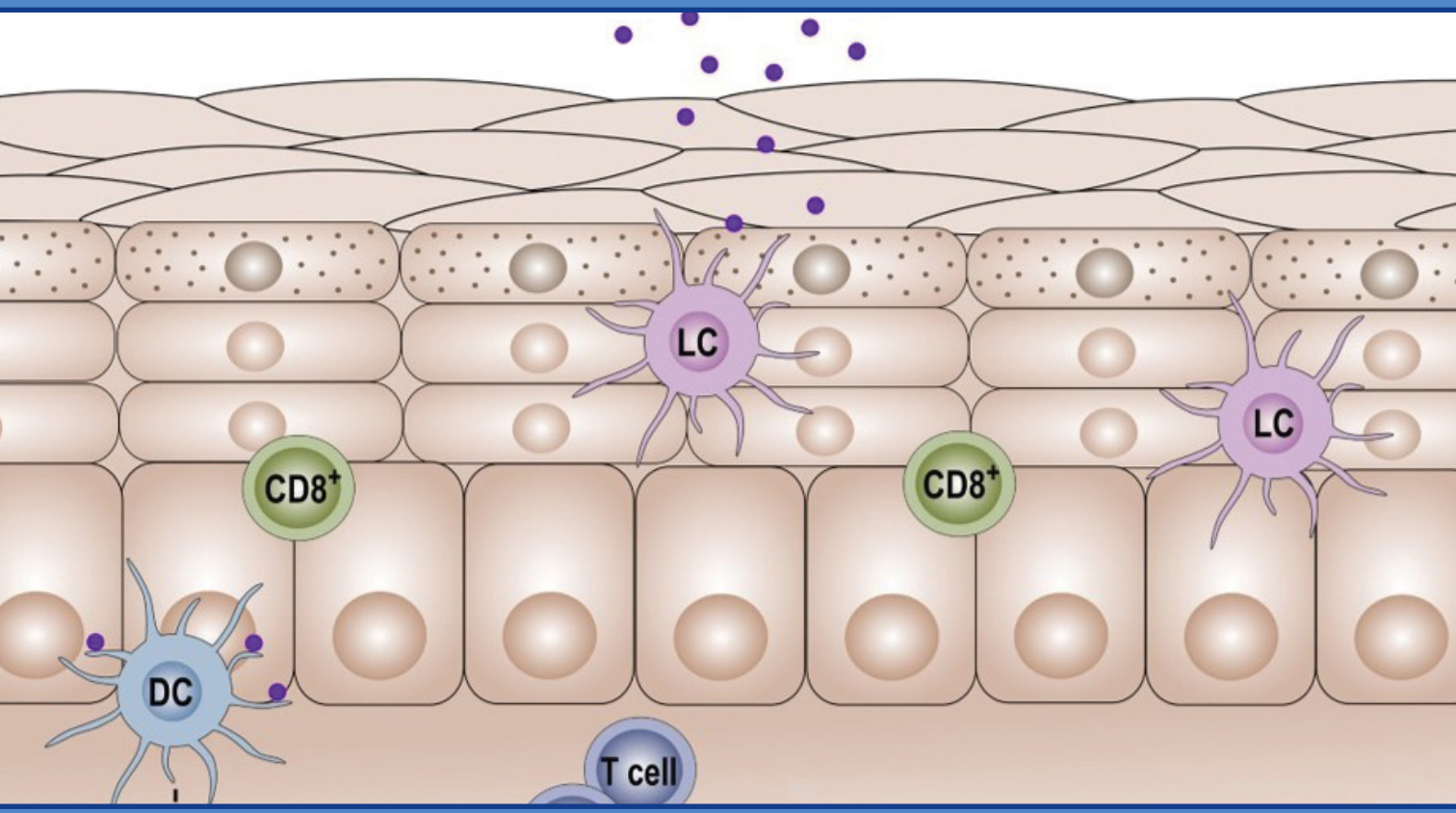
Section B



MECHANISMS OF SKIN ALLERGY

* Genetics of allergic skin diseases
* Mechanisms of immediate-type allergic skin reactions
* Mechanisms of delayed-type allergic reactions
* Interleukins and cytokines in the skin
* Phenotypes, endotypes and biomarkers

1 GENETICS OF ALLERGIC SKIN DISEASES

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Atopic dermatitis, allergic contact dermatitis, and urticaria are the most common types of allergic skin disease. Inherited genetic susceptibility in interaction with environmental factors determine the risk of development of skin allergy in an individual. The clinical manifestations of these diseases usually involve a complex interplay between skin barrier impairment and immune dysregulation that are determined by underlying susceptibility genes. In addition to candidate gene association studies, large scale genome-wide association studies have led to the discovery of novel genetic susceptibility and improved understanding of disease mechanisms.

KEY MESSAGES

- Complex interplay between genetic factors regulating immune responses and skin barrier integrity underlie the pathogenesis of allergic skin diseases
- Genome-wide association studies have identified 31 risk loci for atopic dermatitis that are involved in immune, autoimmune, and skin barrier regulation
- Variants in the filaggrin gene are still the most replicated and strongest genetic risk factors for atopic dermatitis
- Studies of the genetics of allergic contact dermatitis and urticaria have been limited to date
- Genome-wide association studies are needed to understand genetic mechanisms involved in the development of allergic contact dermatitis and urticaria

ATOPIC DERMATITIS

Classically, atopic dermatitis (AD) was thought of as an immune driven disease; however, the discovery of loss-of-function variants in the filaggrin gene (*FLG*) in 2006 as a significant risk factor for AD caused a rapid paradigm shift towards the involvement of dysfunctional epidermal barrier in disease pathogenesis. Filaggrin (filament-aggregating protein) is a major structural protein in the stratum corneum important for cornification, skin hydration, and antimicrobial peptides function. Loss-of-function variants within *FLG* are the strongest and most replicated genetic risk factor for AD development (meta-analysis overall odds ratio for AD ranging from 3.12 to 4.78). It has been estimated that up to 50% of eczema patients are carriers of at least one *FLG* variant, which is associated with an estimated population-attributable risk of approximately 10%. In regard to other AD susceptibility genes, multi-ancestry genome-wide association studies (GWAS) have now identified 31 AD risk loci to date. To further understand the genetic involvement in the atopic march, a concept suggesting the sequential progression from early-onset eczema to asthma and rhinitis, a multi-stage genome-wide association study has also identified seven susceptibility loci involved in the atopic march (Table 1). Thus far, identified AD risk loci include genes with roles in both immune response regulation and epidermal barrier integrity. Notably, some of the newly discovered susceptibility loci are related to autoimmune regulation, linking the pathogenesis of AD, in part, to other autoimmune and inflammatory diseases.

TABLE 1

Susceptibility loci associated with atopic dermatitis and atopic march at genome-wide level		
SNP ID	**Nearest gene(s) symbol**	**Full name of susceptibility gene(s)**
Top ten atopic dermatitis loci		
rs61813875	*CRCT1/LCE3E (FLG)*[†]	*CRCT1*: cysteine rich C-terminal 1; *LCE3E*: late cornified envelope 3E
rs10791824	*OVOL1*	ovo like transcriptional repressor 1
rs12188917	*RAD50/IL13*	*RAD50*: RAD50 double strand break repair protein; *IL13*: interleukin 13
rs6419573	*IL18R1/IL18RAP*	*IL18R1*: interleukin 18 receptor 1; *IL18RAP*: interleukin 18 receptor accessory protein
rs2212434	*C11orf30/LRRC32*	*C11orf30*: Chromosome 11 Open Reading Frame 30 (EMSY transcriptional repressor, BRCA2 interacting); *LRRC32*: leucine rich repeat containing 32
rs4809219	*RTEL1/TNFRSF6B*	*RTEL1*: regulator of telomere elongation helicase 1; *TNFRSF6B*: TNF receptor superfamily member 6b
rs2918307	*ADAMTS10/ACTL9*	*ADAMTS10*: ADAM metallopeptidase with thrombospondin type 1 motif 10; *ACTL9*: actin like 9
rs2041733	*CLEC16A*	C-type lectin domain containing 16A
rs12730935	*IL6R*	interleukin 6 receptor
4:123243592[‡]	*KIAA1109 (IL2)*[‖]	Transmembrane Protein KIAA1109
Atopic march[*] loci		
rs12081541	*CRNN/LCE5A*	*CRNN*: cornulin; *LCE5A*: late cornified envelope 5A
rs17690965	*IL4/KIF3A*	*IL4*: interleukin 4; *KIF3A*: kinesin family member 3A
rs9357733	*EFHC1*	EF-hand domain containing 1
rs479844	*AP5B1/OVOL1*	*AP5B1*: adaptor related protein complex 5 subunit beta 1; *OVOL1*: ovo like transcriptional repressor 1
rs2155219	*C11orf30/LRRC32*	*C11orf30*: Chromosome 11 Open Reading Frame 30 (EMSY transcriptional repressor, BRCA2 interacting); *LRRC32*: leucine rich repeat containing 32
rs993226	*SLC6A15/TMTC2*	*SLC6A15*: solute carrier family 6 member 15; *TMTC2*: transmembrane and tetratricopeptide repeat containing 2
rs10445308	*IKZF3*	IKAROS family zinc finger 3

SNP: single nucleotide polymorphism.
[†] The identified variant is closest to LCE3A, but the previous association with FLG is within 250 kb.
[‡] A nearby SNP rs6827756 in linkage disequilibrium showed similar association.
[‖] The identified variant is within an intron of KIAA1109, but the previous association with IL2 is within 150 kb.
[*] Atopic march, defined as early onset atopic dermatitis (up to 3 years of age) followed by childhood asthma (up to 16 years of age).

ALLERGIC CONTACT DERMATITIS

The understanding of the genetics of allergic contact dermatitis (ACD) is evolving, with most existing studies taking a 'candidate gene' approach and focusing on genetics of immune mechanisms in ACD. Amongst ACD candidate genes, variants in the tumor necrosis factor gene (*TNF*) have been the most investigated genetic risk factors for ACD. In addition, variants in *NAT1*, *NAT2*, *GSTM1*, *GSTT1*, ACE, TNFS, and the IL-16A genes have been associated with ACD. A GWAS failed to identify genetic variants that met the genome-wide statistical significance threshold; however, variants in the *NTN4* and *PELI1* genes demonstrated the potential for association with allergic nickel dermatitis.

URTICARIA

Studies on the genetics of urticaria are very limited. Among three families affected by cold-induced urticaria, three distinct in-frame deletions in *PLCG2* genes showed co-segregation with the disease. A GWAS on NSAID-induced acute urticaria reported no genome-wide significant associations, but there was suggestive evidence that variants in *HLF*, *RAD51L1*, *COL24A1*, *GalNAc-T13*, and *FBXL7* genes could be associated with the disease.

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2 MECHANISMS OF IMMEDIATE-TYPE ALLERGIC SKIN REACTIONS

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KEY MESSAGES

- The mast cell is a skin-resident cell responsible for the immediate allergic skin reactions
- Amplifying mechanisms such as involvement of the nervous system is likely to occur after initial mast cell activation
- Allergic skin reactions can be caused by either external allergen absorption via the stratum corneum, or they can be elicited by redistribution of allergens including auto-allergens

Immediate type (IgE-mediated-) allergic reactions may originate from a number of organs, often close to the borders between the individual and the surrounding environment, i.e. the skin, the mucous membranes of the eyes, the upper and lower airways and the gastro-intestinal tract. Symptoms from the skin are wheals and flares, summarized with the term urticaria [ref. to this Atlas' paragraph on urticaria], whereas conjunctivitis, rhinitis (hay-fever), asthma and a variety of gastro-intestinal symptoms may arise from the other organs.

One single cell-type, the mast cell, is responsible for the immediate skin symptoms and these cells are present in all areas of the skin, albeit in different numbers, where densities are highest on hands, feet and face, i.e. the body parts mostly in contact with the surrounding world (Figure 1). Anatomically the mast cells are found in the superficial layers of the dermis (Figure 2) and the proximity of mast cells to the surface of the skin and the intense vascularization allows diffusion of allergenic molecules to the cells both from the outside and from the blood-stream. Less well studied is the possibility that also nerves may interact with and activate mast cells, and thus account for the fast spreading of the hives sometimes observed when large skin areas become affected by urticaria. The most well-known form of an immediate, exogenous skin-reaction is perhaps the iatrogenic skin-prick tests made for diagnostic purposes, where a small volume of an allergen extract is introduced into the skin by pricking through a droplet of the extract and puncturing the stratum corneum by a tiny lancet. Other forms occur in the form of contact urticaria with epidermal exposure to (often occupational) protein allergens. Urticaria is a common feature of food allergies where the food allergens are believed to be systemically absorbed and the redistributed to the skin causing mast cell activation.

Figure 1 Density of skin mast cells on the surface of the body

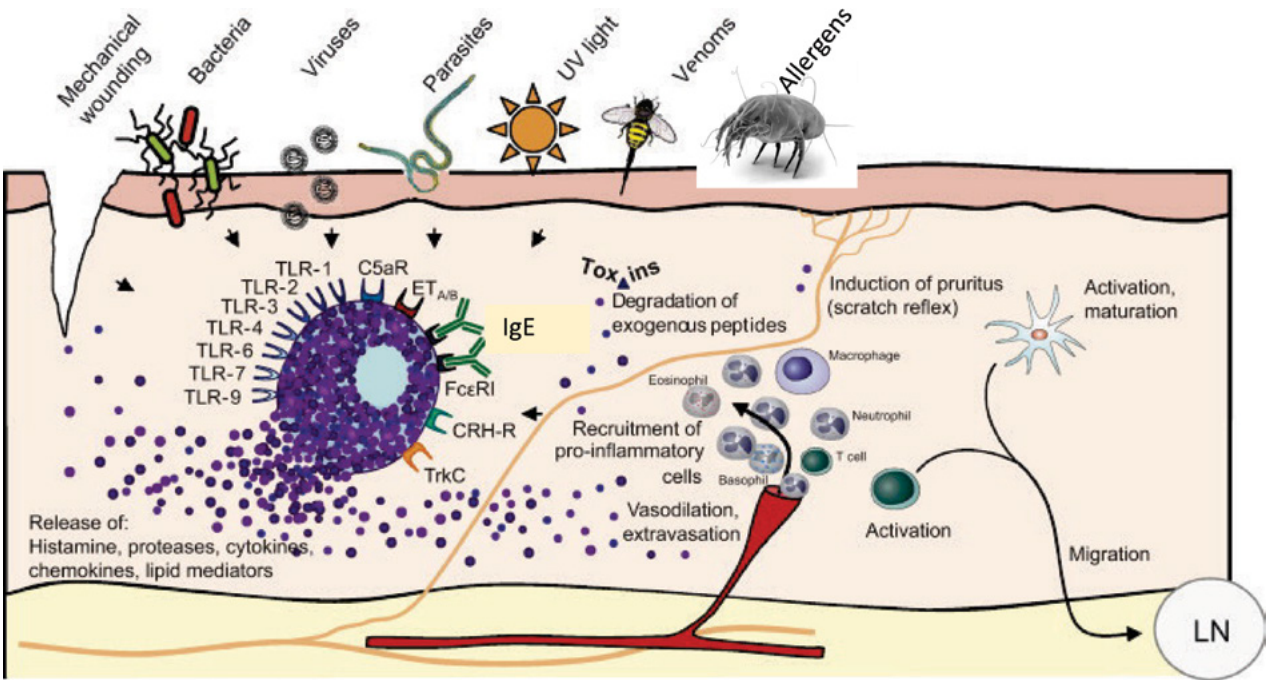

Figure 2 Anatomic drawing of the skin with mast cells, vessels, nerves. Besides activation via receptor-bound IgE, the mast cell also carries a number of other innate immune receptors and receptors for endogenous ligands

The mast cell is a leukocyte derived from pluripotent hematopoietic stem cells, but unlike the closely related circulating granulocytes: basophils, eosinophils and neutrophils, it has longevity and is believed to migrate to the tissues where it finally differentiates. Mast cells each have several hundred thousand IgE-receptors that bind IgE with high affinity, and when a person becomes allergic, allergen-specific IgE attaches to the receptors after which the mast cells and the skin is said to be sensitized.

When an allergen molecule crosslinks FcƐRI-bound IgE on mast cells, cellular activation processes leads to degranulation, mediator release and chemo- and cytokine induction with histamine and leukotriene being the first released mediators (Figure 3). These in turn leads to stimulation of nerve-endings (causing itch), vasodilation (causing redness: the flare) and vascular leakage causing superficial skin edema (wheals, hives).

It is important to realize that not only allergic (IgE-mediated) reactions can activate mast cells, but all forms of skin mast cell activation, may lead to the same type of symptoms, and the diagnosis must establish the cause and mechanism (Figure 2).

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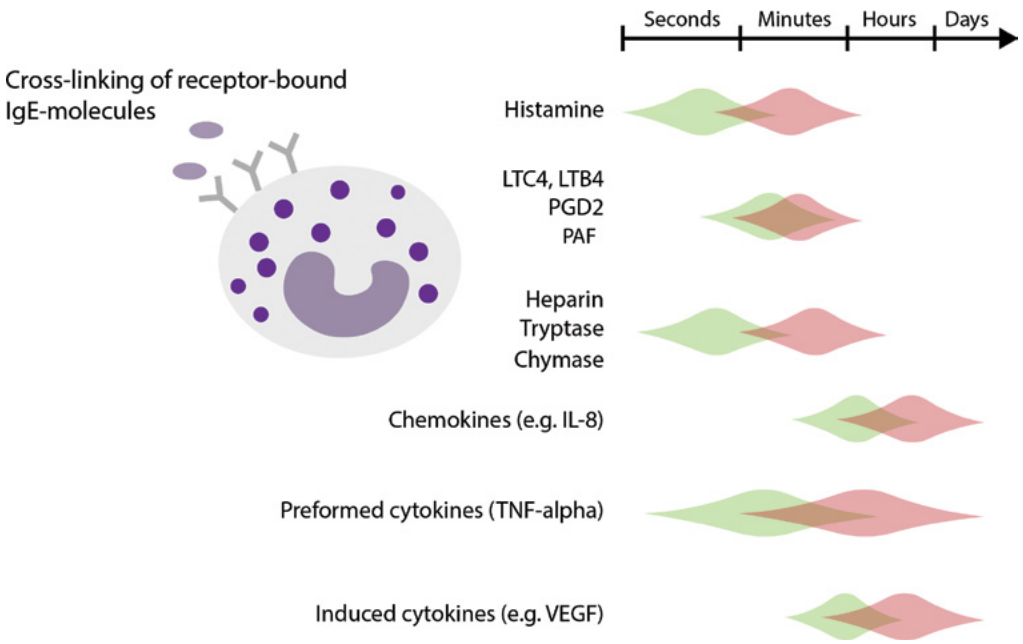

Figure 3 Allergen activation of mast-cell with release of mediators (kinetics for release in green) and the interval where they exert their primary effects (in red). Mediators comprise histamine giving rise to itch, vasodilation, and vascular leakage. The lipid-derived mediators, Leukotriene C4 (LTC4) and Prostaglandin D2 (PGD2) have the same effects as histamine, as have Platelet Activating Factor (PAF), but PAF and LTB4 may also act at chemoattractant for other leukocytes. Most cytokines and chemokines are released only after they have been newly synthesized, and help attracting leukocytes, in particular T-lymphocytes and eosinophils to the site of the activated mast cell. This inflammation is called the late-phase skin reaction and occurs 3-5 hours after the primary activation of the mast cell

3 MECHANISMS OF DELAYED-TYPE ALLERGIC REACTIONS

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KEY MESSAGES

- Delayed-type hypersensitivity reactions are mediated by T lymphocytes that recognise specific antigens
- Polarization of antigen-specific T lymphocytes is determined by the immune micromilieu
- Polarized subsets of T lymphocytes such as Th_1, Th_{17}, and Th_2 cells determine the inflammatory signature of delayed-type hypersensitivity reactions and the clinical phenotype
- Both, antigen-specific skin resident effector memory T lymphocytes and T lymphocytes recruited from the circulation are involved in delayed-type hypersensitivity responses

The original classification of Coombs and Gell categorises hypersensitivity reactions into four subtypes, where the delayed-type is put into type IV (Figure 1). More insights into new mechanisms have led to subclassifications of type IV immune reactions undergoing constant updates (e.g. type IVa ($CD4/Th_1$-mediated), type IVb ($CD4/Th_2$-mediated), type IVc (CD8/cytotoxic T-cell-mediated), and type IVd (CD4/T Th_{17}–mediated with neutrophilic inflammation). Sensitization to proteins, haptens or larger molecules is a prerequisite to all these reactions. The skin is an especially immune-competent organ from which activated antigen presenting cells such as dendritic cells (DC) - following uptake of antigenic material and its processing – migrate to the draining lymph nodes and undergo a process of maturation (Figure 2). There, DC present appropriately sized antigenic structures via MHC I to CD8+ T lymphocytes or via MHC II to CD4+ T lymphocytes. MHC molecules bind with their T cell counterpart- the T cell receptor (TCR) that consists of one α and one β chain. In the presence of co-stimulatory molecules and the appropriate immune micromilieu, effective binding will lead to activation of T lymphocytes, leading to their proliferation (Figure 2, Figure 3). In addition, these T cells, that have been activated for the first time undergo polarization, leading to distinct immune phenotypes and qualities (Figure 4). Main determinants for the qualitative outcome in regard to immune profiles are the different antigens, different co-stimulatory molecules and most importantly, the immune micromilieu. Exposure to interleukin (IL)- 12 drives polarization towards a Th_1 phenotype. Th_1 T cells produce IFN-γ, TNF and IL-2. In CD8+ so-called cytotoxic T cells, a similar phenotype can be detected termed Tc_1. A micromilieu dominated by inflammatory cytokines such as IL-1, IL-6, IL-23 with and without TGF-β will favor a development of IL-17 producing Th_{17} cells. The therapeutic success of targeting type 2 immune cytokines IL-4 and IL-13 in atopic eczema demonstrates that also Th_2 and Tc_2 cells can be crucially involved in delayed-type hypersensitivity reactions of the skin. Interestingly, a major effector cytokine IL-4 is also the main driver of type 2 polarization.

Following sensitization, re-exposure to the eliciting allergens will mount a delayed type cutaneous immune response detectable as eczema or exanthema. Cutaneous exposure to recall antigens recruits and activates T lymphocytes in the skin. For a long time,

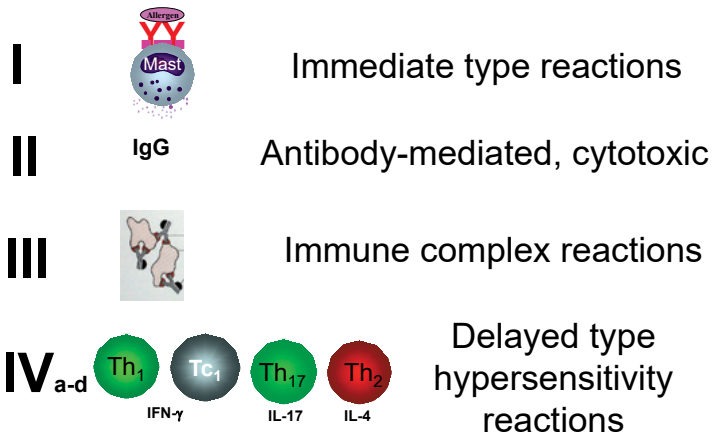

Figure 1 Immune reactions according to Coombs and Gell - Categorising immune reactions into four different types has become the basis of teaching immunology. Among the delayed-type hypersensitivity reactions, of which delayed-type allergic reactions of the skin are subtype, different clinical pattern have been charaterized and associated with the respective immune phenotypes

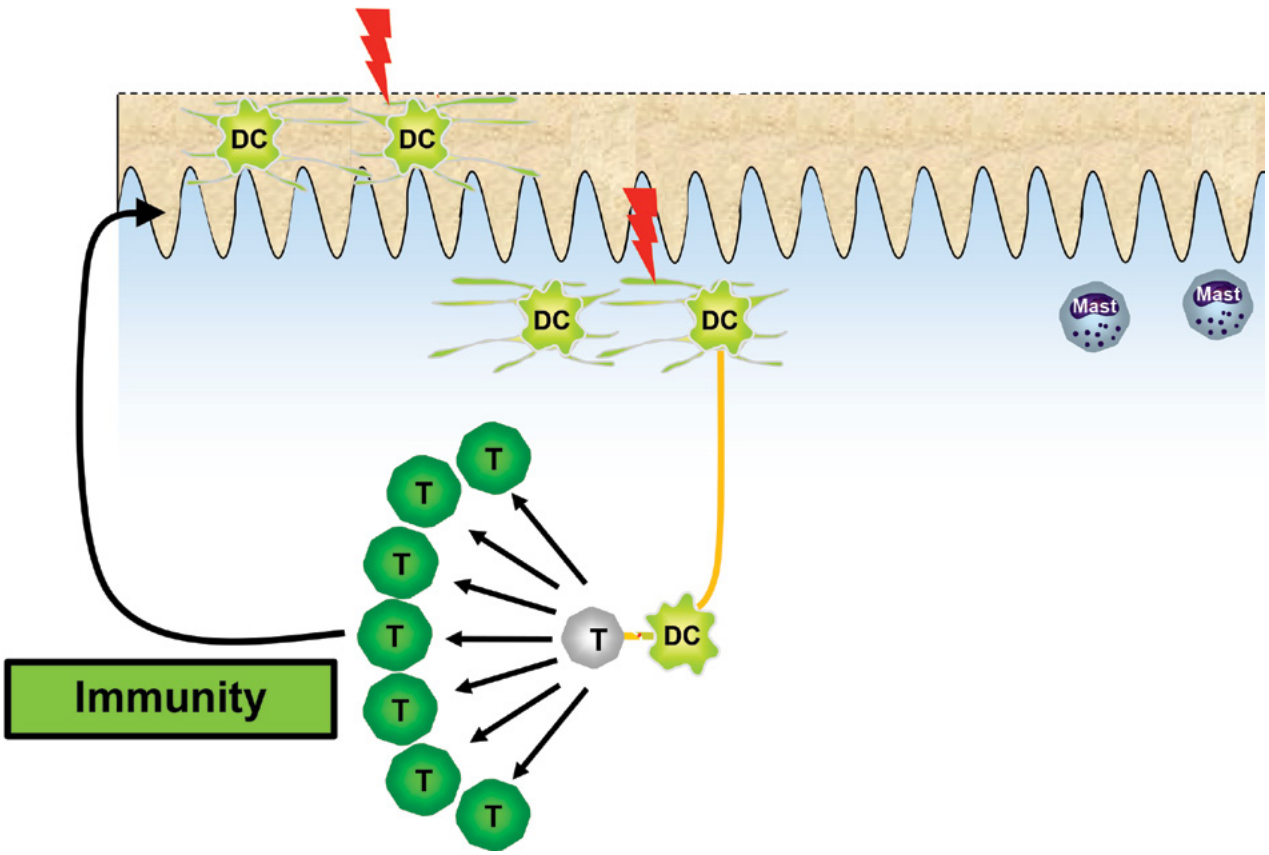

Figure 2 Sensitization through the skin - Ever since Edward Jenner established small pox vaccination leading to the eradication of this desease in the 1980s it was evident that the skin is a very potant immune organ. We understand that different types of dendritic cells (DC) reside in the skin ready to scan for information and especially danger signals that they capture with their dendrites. Receiving the appropriate activation stimuli these dendritic cells migrate to the draining lymph nodes where they look for their appropriate partner (T cell receptor of a T cell) which they can stimulate for proliferation

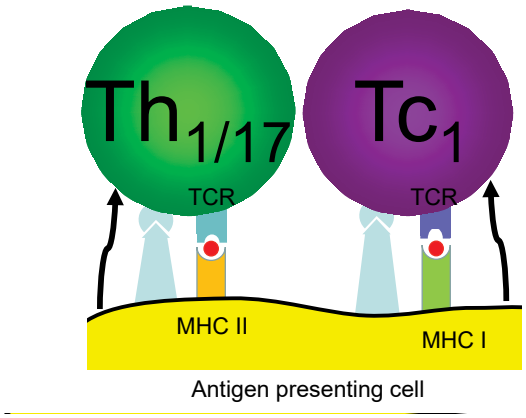

Figure 3 The immune synapse: Players and consequences -The interplay between antigen presenting cells such as DC and CD4+ or CD8+ T cells relies on the binding of the appropriate T cell receptor (TCR) to antigen (red circle) loaded MHC class II or MHC class I molecules. Together with this binding costimulatory molecules (light blue symbols) must lead to a signal within the T cells to allow activation and proliferation. Along with these signals the immune micromilieu (arrows) will activate and orchestrate the signals leading to T cell polarization (e. g. Th_1, Th_{17}, Tc_1, ...) into different immune phenotypes, that later determine the clinical course of the delayed allergic immune reaction

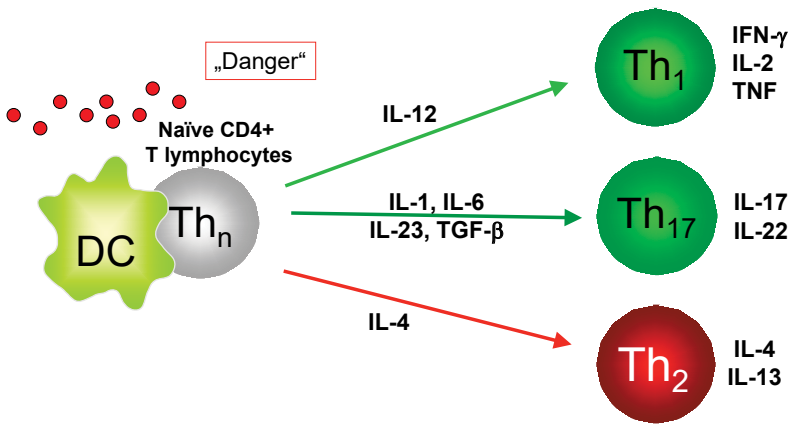

Figure 4 Initiation and characterization of immune phenotypes - As described and shown in figures 2 and 3, activation of naive CD4+ T lymphocytes depends on various incoming signals. For the immune phenotype polarisation, the immune micromilieu is most important for the outcome. To obtain Interferon (IF-) γ, IL-2, and TNF producing Th_1 cells, IL-12 is the most potant inducer. For Th_{17} cells producing IL-17 and also IL-22, IL-1, IL-6, IL-23 with and without TGF-β are important. The IL-4 and IL-13 producing Th_2 cells are most dominantly induced by the type 2 cytokine IL-4 itself

this was believed to be the only mechanism of delayed type allergic reactions in the skin. More recent analyses, however, demonstrated that antigen experienced memory T cells can also reside within the skin and may be activated directly within the skin to mount a typical delayed-type hypersensitivity response. It is likely that epicutaneous patch testing, atopy patch testing, and delayed responses following intracutaneous testing rely on the presence of antigen experience memory T lymphocytes to develop eczematous skin inflammation (Figure 5). Downstream of activated cutaneous T cells producing their effector cytokines resident effector immune cells, activated surrounding stroma and endothelial cells allow transmigration of newly arriving immune cells to amplify the response and make it clinically visible. Based on the immune phenotype of antigen-specific T cells, different clinical pictures will develop. Type 1 immune cytokine-dominated delayed-type immune responses of the skin will present as eczema or maculo-papular rashes; type 17 dominated immune reactions will present with neutrophils visible even as pustules; type 2 dominated immune responses often present with an initial edematous flare and a susceptibility to cutaneous infections, even yellow crusts rich of *Staphylococcus aureus*; and purely T cytotoxic immune responses will lead to an immune reaction pattern called interface dermatitis as seen in lupus, lichen planus, and certain types of drug reactions such as fixed drug eruptions, erythema, multiforme including very severe types of drug reactions.

An understanding of the mechanisms underlying delayed-type allergic skin reactions allows us to better diagnose, interpret, and identify major cytokines involved, and to consequently better plan interventions for delayed-type allergic skin reactions.

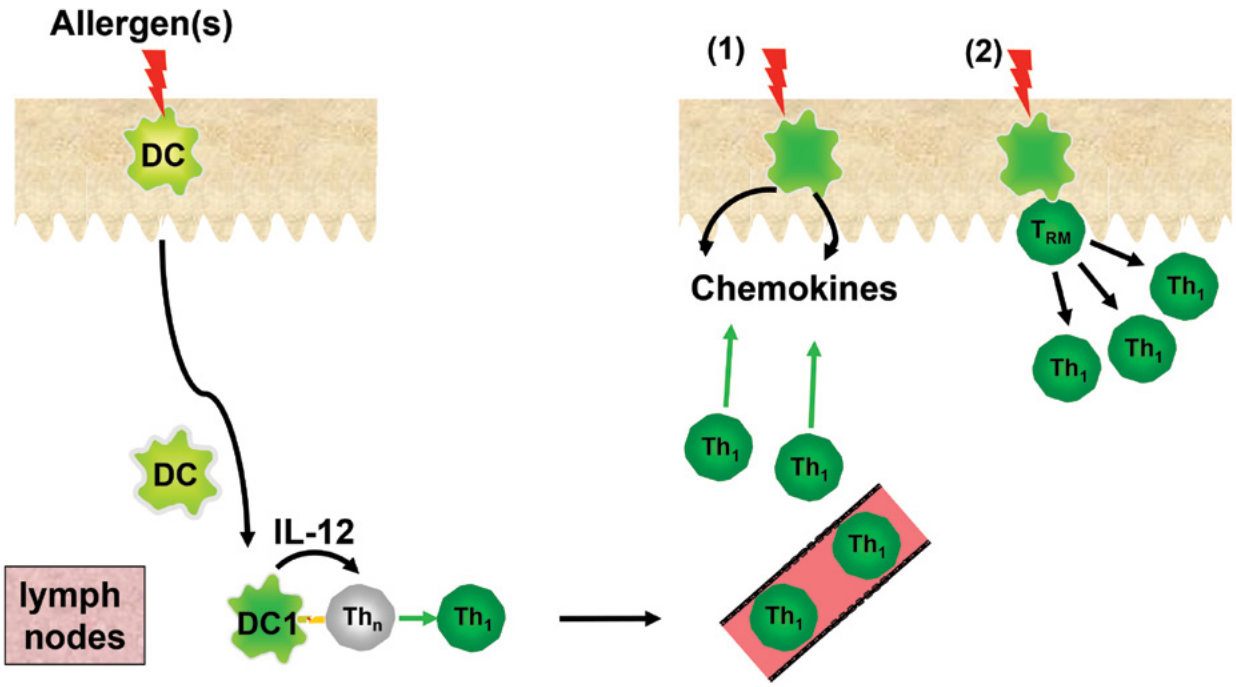

Figure 5 Scenarios of elicitation of delayed type allergic reactions of the skin - Cutaneous delayed-type allergic reactions of the skin may be elicited by systemic exposure (drug administration) or cutaneous exposure to the allergen. For the latter, the exposure is believed to activate initial cells within the skin leading to the recruitment of newly arriving antigen experienced memory T cells eliciting disease. More recently it became evident that following sensitization (left), antigen experienced memory T cells are distributed not only to the site of sensitization but also to other skin sites allowing them to directly respond to cutaneous exposure to allergen. These T cells are called tissue resident memory T cells (T_{RM}). The concept of skin T_{RM} cells may also explain why delayed allergic reactions of the skin to certain drugs repeatedly developed within the skin but apparently less frequently within other organs

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4 INTERLEUKINS AND CYTOKINES IN THE SKIN

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OVERVIEW

Interleukins and cytokines are small secreted peptide mediators that orchestrate the interaction between lymphocytes, monocytes or macrophages and the tissue including keratinocytes. The systematic analysis of skin diseases highlighted that interleukins and cytokines are elementary to the understanding of the pathogenetic process and allow the categorization into 4 fundamental classes: Pattern 1 characterized by IFN-γ and TNF-α and a lichenoid appearance, pattern 2 characterized by type-2 interleukins IL-4, IL-5, IL-13 and IL-31 covering atopic eczema, pattern 3 contains IL-17A, IL-17F, IL-21 and IL-22 and covers psoriasis and finally group 4 with IL-10 and TGF-β that covers fibrotic diseases.

KEY MESSAGES

- Interleukins and cytokines are secreted mediators that are representing critical elements in molecular skin disease categorization
- 4 different skin diseases can be classified on the basis of the immune-phenotype
- Interleukins are not only produced by infiltrating cells, but also by keratinocytes

INTERLEUKINS & CYTOKINES PRODUCED BY INFILTRATING CELLS

The infiltration of tissues by immune cells allows the host a complex variety of responses that exceeds the pure barrier function of the skin including differential responses between harmless and potentially dangerous pathogens. Interferons and TNF are produced by dendritic cells functioning as skin resident sentinels able to respond to bacterial or viral triggers and recruit other cells. Therefore, they are thought to be at the beginning of an inflammation process and IL-1 as well as IL-6 are prototypic early response mediators. Dendritic cells are also able to present antigens to T cells and among the resulting phenotypes IL-17 secreting Th17 cells are important early mediators of inflammation. IL-17 induces IL-8 in keratinocytes that recruit neutrophils to the site of activation. Th22 cells are particularly enriched in epithelial layers and play an important role in the regeneration of epithelial surfaces by secretion of IL-22. Allergic disease type-cytokine (IL-4, IL-5, IL-9, IL-13, IL-31) secreting cells are characteristic and can be used for specific diagnosis. The antigen-driven activation of Th1, Th2 and Th17 cells is amplified by innate lymphoid cells (ILCs), which themselves do not express an antigen specific receptor, but can produce cytokines that further drives the characteristic inflammation. Interestingly ILCs can recognize signals from keratinocytes such as IL-33 that activates them for IL-4 secretion. While the secretion of these “allergic”cytokines are primarily observed following recent antigen contact/challenge, there is also production of interleukins and cytokines of tissue resident cells (Figure 1).

INTERLEUKINS & CYTOKINES PRODUCED BY KERATINOCYTES

Tissue resident macrophages and dendritic cells are well known sentinels and migrate upon activation to the lymph draining lymph node

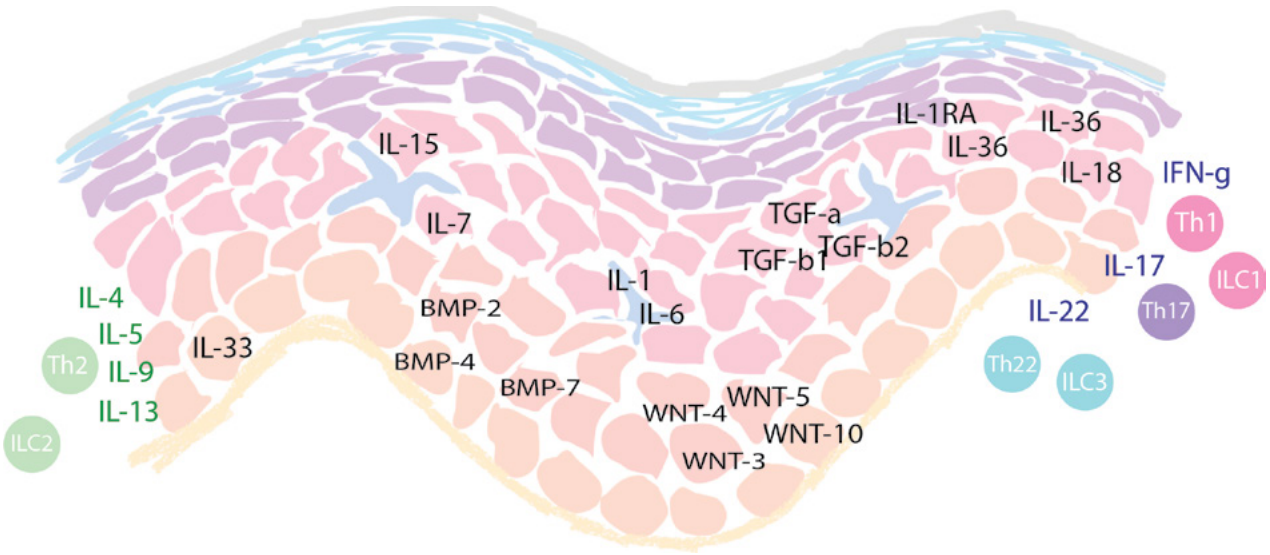

Figure 1 The schematic scheme shows the different levels of keratinocytes that are themselves source of many cytokines and interleukins. Main infiltrating cells along with their secretion products are shown on the left and on the right side of the scheme

to further activate lymphocytes. However also the immobile keratinocytes produce cytokines such as the IL-33 that promotes type-2 immune reactions, but also IL-18, that promotes type-1 immunity. Keratinocytes also provide IL-7 and IL-15 for the survival of infiltrated lymphocytes. Furthermore, they secrete TGF-α and -β as well as other cytokines of this TGF-superfamily such as BMP2, 4 and 7. These factors are assumed to play an important role in matrix formation, but can also play a role in immune suppression. The keratinocyte derived WNT-cytokines (WNT2b, 3, 4, 5, 7, 10, 11) are likely to play a role in the differentiation of basal keratinocytes. The differentiation also determines which immunological windows are active and ongoing research (in particular single cell sequencing) indicated that for example receptors and antagonist of inflammasome related genes are active in later differentiation, while absent in basal keratinocytes. Therefore, immune system and keratinocyte differentiation are forming an interdependent network that may determine the type and the duration of the inflammation. An exception is type-2 related IL-33 that is present in early stages but absent in later stages.

SUMMARY

Interleukins and cytokines of the skin fall into 4 characteristic classes and are subject to biological therapies. Current research and future therapies may also take advantage of keratinocyte-derived cytokines as they are important for the barrier function and the feedback to the immune system and may also be important for the chronicity of the disease.

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5 PHENOTYPES, ENDOTYPES AND BIOMARKERS

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KEY MESSAGES

- The endotype-driven approach offers a way to better diagnose, monitor, and stratify patients based on pathogenetic mechanisms
- Biomarkers are the mainstay of stratified medicine. A good biomarker should link the disease endotypes to the visible properties, while proving validity (reproducible, easy to measure and cost-efficient) and relatedness to a clinical end-point
- The deep learning-based molecular disease classification can be used to guide decisions made on the diagnosis and treatment of allergic diseases, and therefore may have important applications in precision medicine

At present, management guidelines for allergic diseases are based on the evaluation of symptoms, target organ function, exacerbations, need for rescue medication, and limitation of quality of life, all the while reinforcing the importance of achieving disease control and reducing future risk. The "one size fits all" approach of current guidelines does not address the complexity of allergic diseases resulting from the heterogeneous and dynamic combination of dysregulated innate and adaptive immune response, chronic inflammation, tissue remodeling, and hyperresponsiveness in affected tissues. The management options available today only offer relief of symptoms and do not cure the disease, making it increasingly clear that new approaches are required. Accordingly, the precision medicine approach for allergic diseases is continuously developing (Figure 1).

Disease phenotypes cluster together relevant visible properties such as age at onset, triggers, co-morbidities, physiologic traits, remodeling, inflammation type (eosinophilic and non-eosinophilic), and treatment response. Phenotypes do not necessarily relate to or give insights into the underlying pathogenetic mechanism. In addition, they frequently overlap and are subject to change over time. Thus, defining disease endotypes based on key pathogenetic mechanisms has become a rational development as the endotype-driven approach offers a way to better diagnose, monitor, and stratify patients (Figure 1).

Biomarkers, or biological markers, are the mainstay of stratified medicine allowing classifying individuals into subpopulations that differ in their susceptibility to a particular disease or in their response to a singular treatment. Biomarkers belong to a broad category of biological characteristics used to examine normal biological or pathological processes and responses to therapeutic or prophylactic intervention that can be measured accurately and reproducibly. The use of biomarkers in basic and applied research as well as in clinical practice has become so commonplace that their presence as endpoints in clinical trials and even their use in daily practice is now accepted almost without question. A good biomarker should link the disease pathogenic mechanisms (endotypes) to the visible properties (phenotypes), while proving validity (reproducible, easy to measure and cost-efficient) and relatedness to a clinical end-point. Currently, most biomarkers for al-

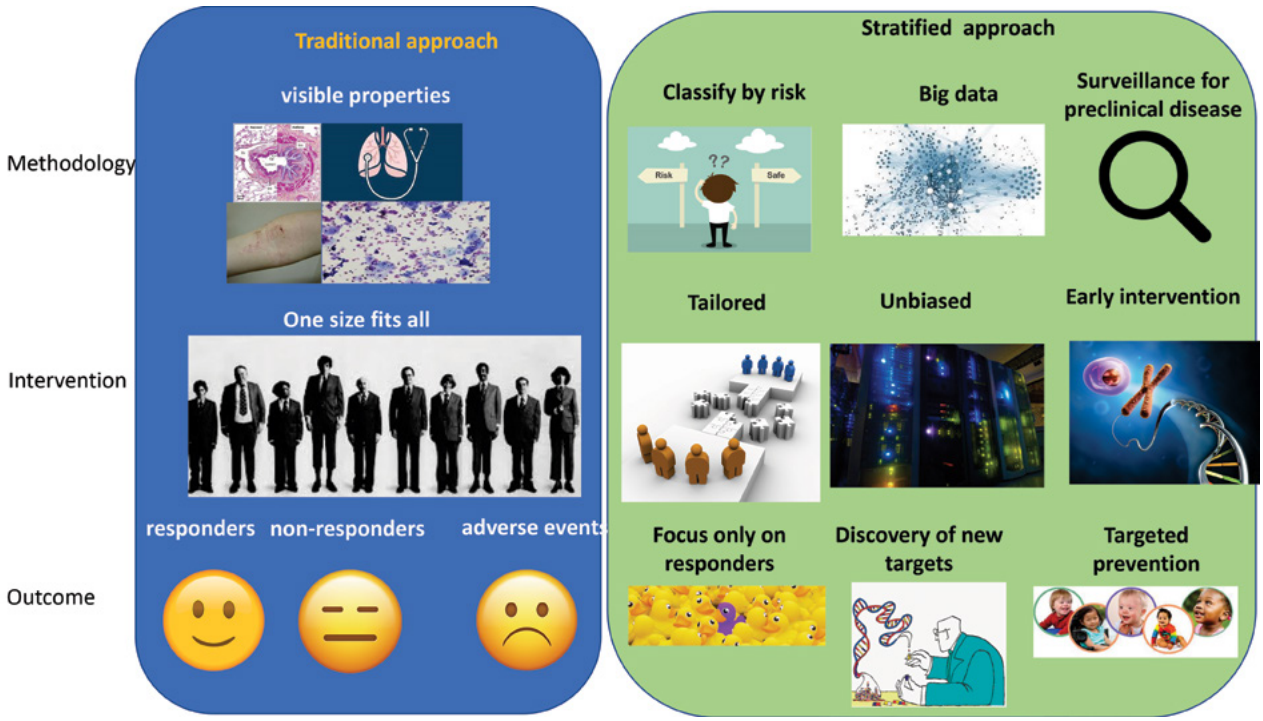

Figure 1 Comparisons between the traditional current approach and the precision medicine/stratified approach

lergic diseases require further objective validation and qualification by regulators to be used in clinical practice.

Omics is the holistic approach of studying genes and their epigenetic regulation, phenotypes, lipids, enzymes, metabolic processes, and neural connections (Table 1). During recent years, a huge amount of omics data has been developing and can only be rationally analysed in-depth with a cooperation between biologists, data scientists, and healthcare professionals. The deep learning-based molecular disease classification can be used to guide decisions made on the diagnosis and treatment of allergic diseases, and therefore may have important applications in precision medicine. A core element of a systems biology approach is development of in silico computational models (mechanistic models) by means of integration of different types of experimental and clinical data from multiple studies, including those associated with disease conditions. In silico experiments (ie, computer simulations or mathematical analysis of in silico models) can test model-specific hypotheses, predict disease prognosis or treatment outcomes, and identify knowledge gaps, guiding future experiments and clinical trials that produce further data. This iterative process refines in silico models, providing holistic systems-level mechanistic insight into how perturbations (treatments or risk factors) lead to phenotypes and endotypes. Existing mechanistic models of AD vary widely, depending on the levels of interaction (tissue, cells, proteins, and genes) included in the model and mathematical methods used to describe the interactions. Domínguez-Hüttinger et al developed a multi-scale deterministic model that delineates interactions between the environment, skin barrier integrity, and immune activation using ordinary differential equations. Two "switches" are described: the first regulating the onset of AD flares and the second controlling progression to severe and persistent disease. The model predicts, for example, that genetic predisposition to barrier dysfunction (eg, FLG haploinsufficiency) predisposes to longer flares and more persistent disease and that prophylactic emollient use might be beneficial. The development of more sophisticated human and computational models of AD that integrate large-scale clinical and "omics" data offer the potential for a deeper understanding of disease endotypes, molecular mechanisms

TABLE 1

Main omics areas with specific domains and tools uses

Omic area	Domain	Technologies used
Genomics	genes, exons, introns, promoters, transcription factors, and many other genome-related functions.	Next generation sequencing (i.e. Illumina HiSeq), Sanger sequencing, *de novo assembling*, bioinformatics.
Transcriptomics	All RNA molecules in one cell or a population of cells.	Next generation sequencing (RNA sequencing), bioinformatics, microarrays, real-time PCR.
Proteomics	Set of proteins produced in an organism, system, or biological context (expression; production, degradation, and steady-state abundance; interaction with each other; movement within intracellular compartments; involvement in metabolic pathways	Enzyme-linked immunosorbent assay (ELISA), mass spectrometric immunoassay (MSIA)
Metobolomics	Metabolome or the secondary metabolites of an organism, such as amino acids, sugars, phosphates, nitrogen containing compounds, polyols, etc.	Gas chromatography fused with mass spectrometry (GC-MS), liquid chromatography fused with mass spectrometry (LC-MS).
Lipidomics	Cellular lipids of an organism or a biological system.	Electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI).
Catalomics	Enzymes (catalysts) or other biocatalysts of an organism or a system.	"Click" reactions in chemistry with activity-based protein profiling (ABPP), posttranslational modifications (PTMs) and enzyme inhibitor developments

underlying key pathogenic events and clinical hallmarks of AD, as well as prediction of therapeutic outcomes, including comorbidity at the level of an individual patient. However, these models are based on a reductionist approach, and they need to be perfectioned in order to reflect the complexity of AD pathogenesis, including epidermal barrier dysfunction, altered penetration of chemicals and allergens, host/environment interaction, type 2 and non-type immunity, and tissue remodelling.

Precision endotyping that links pathobiological mechanisms with visible properties via specific biomarkers and can be translated into pathway-specific diagnostic tests opens a pathway to accurate disease classification and individualised targeted treatments. It is expected to change the diagnostic and therapeutic landscape of all medical disciplines. However, the endotype-driven approach still needs to overcome multiple challenges before its implementation in the management of allergic diseases in daily practice (Table 2).

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TABLE 2

Major directions in improving the endotype-driven approach in allergic diseases
Type 2 and non-type 2 allergic disease profiling should involve the interconnected concepts of phenotype-biomarker- dynamic complex endotype, while expanding towards new targets such as epithelial and neurogenic components, and epigenetic modifications.
To confirm the validity of an endotype, longitudinal follow-up studies of clinical and molecular profiles need to be performed.
Early endotyping of milder or at-risk patients might provide more insight into disease mechanisms.
A revised taxonomy of allergic diseases based on precision medicine and endotype profiling is necessary to stimulate targeted research and identify biomarkers that can predict patient response to treatment.
Collaboration of healthcare providers with pharmaceutical and biotechnical companies, scientific organizations, and governmental regulatory agencies will play a crucial role in supporting innovative approach to bring precision/stratified medicine closer to the clinic.

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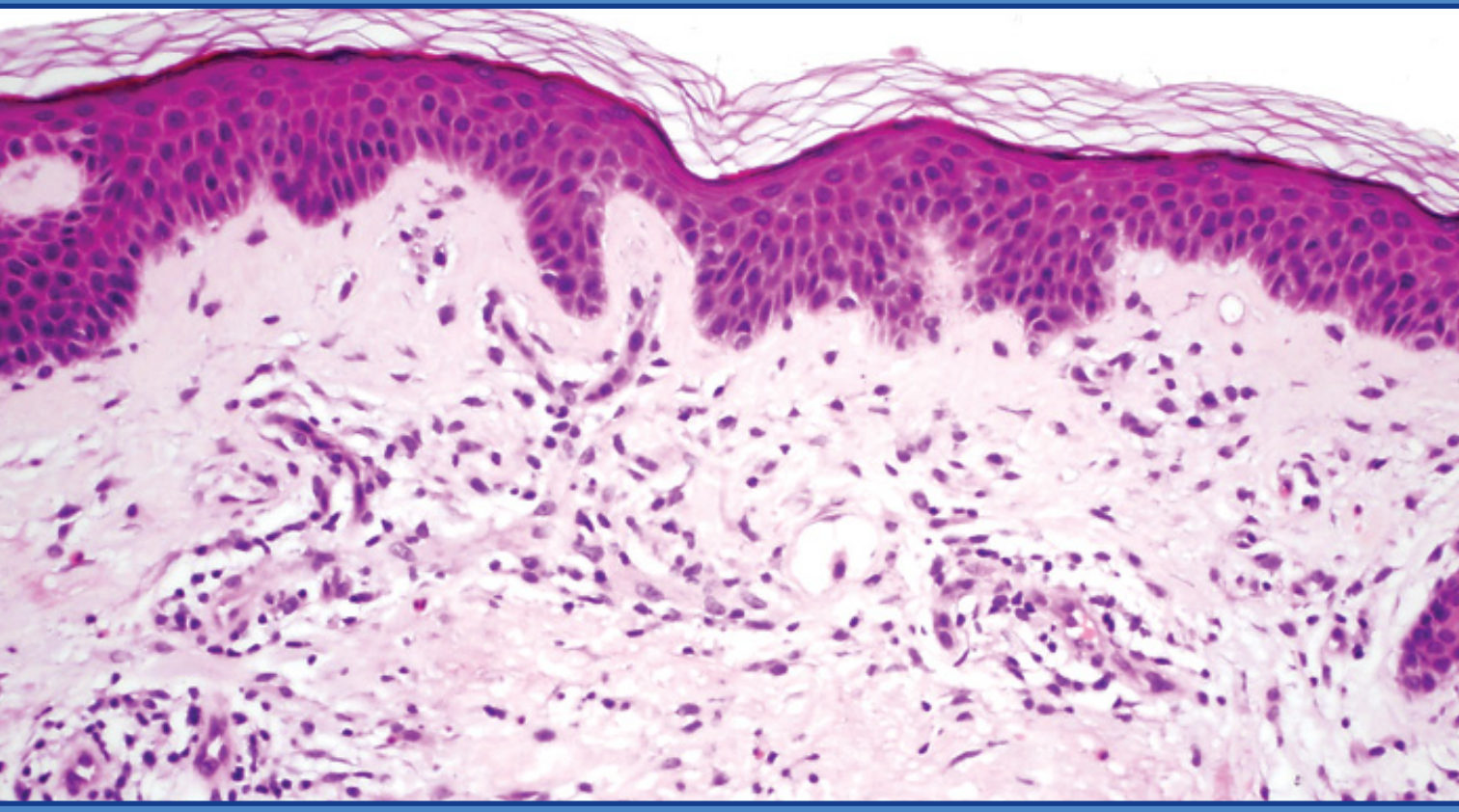
Section C



MORPHOLOGY AND DIFFERENTIAL DIAGNOSIS OF ALLERGIC SKIN DISEASES

* Nomenclature of skin lesions, morphology and distribution patterns
* Histopathology
* Dermatological differential diagnosis of allergic skin reactions

1 NOMENCLATURE OF SKIN LESIONS, MORPHOLOGY AND DISTRIBUTION PATTERNS

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KEY MESSAGES

- The differential diagnosis of allergic skin diseases is not always easy
- Correct classification of allergic skin diseases by morphology and distribution patterns is a prerequisite for interpreting data from different studies
- Primary and secondary skin lesions, morphological descriptions and distribution patterns constitute the essential foundation for diagnosis and phenotyping
- Basic recognition of dermatological primary and secondary skin lesions as well as use of correct nomenclature for morphological dermatological descriptions have to be known also by non-dermatological allergists dealing with allergic skin diseases

The skin is the most frequently involved and most visible organ in allergic reactions. Correct classification of allergic skin reactions into well-defined entities strongly depends on a good understanding of lesion morphology, nomenclature and distribution patterns as well as thorough clinical examination and correct description of morphological features of the skin. Primary and secondary skin lesions, morphological descriptions and distribution patterns constitute the essential foundation for later diagnosis (Table 1, Table 2). Morphology is more reliable, if assessed by an experienced physician in the acute phase and a dermatologist may be needed for differential diagnosis, but photography of the clinical reaction by the patient (e.g. smartphone) can be very helpful and should be asked for. Disease extent is categorised either as generalised, i.e. widespread lesions where no major regions of skin are exempt, disseminated, if different skin regions involved, or localised with lesions limited to a certain area of the body. A skin "rash" has lesions, which are discrete (isolated), confluent (coming together) or diffuse (forming areas without islands of uninvolved skin) (Table 2). Demarcation of the lesions may be sharp (as in urticaria) or non-sharp (as in eczema).

The most common diseases in skin allergy are urticaria, maculopapular exanthema (MPE) and eczema. Urticaria is characterised by wheals, circumscribed areas of raised erythema and oedema of the superficial dermis and a fleeting nature, with resolution of a single lesion within 24 h (Figure 1A) , whereas continual appearance of new lesions is common. Angioedema often affects the face, hands, feet or genitalia with an oedema of the deeper dermis +/- subcutis and has slower resolution. An exanthem is an erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules with different degrees of confluence (Figure 1B). Lesions persist for several days. MPE is the most common entity, but other entities where exanthems are associated with blisters, pustules, or special distribution have to be ruled out. Eczema is an inflammatory skin disease with typical histopathologic changes (e.g. epidermal spongiosis, acanthosis, parakeratosis superficial dermal perivascular lymphohistiocytic infiltrate) and clinical manifestations (non-sharply delineated erythema, papules, blisters, weeping and crusting in the acute stage and sebostasis, induration, lichenification, excoriation and scale in

TABLE 1

Dermatological primary and secondary skin lesions in allergic skin diseases	
Angioedema	Transient soft swelling by a deep dermal and/or subcutaneous edema
Bulla (blister)	Larger (>5mm in diameter) elevated circumscribed lesion filled with clear fluid leading to detachment of the epidermis
Crust	Dried serum, blood or pus on the skin
Erythema	A large area arising from vascular dilation causing redness
Erosion	Partial loss of epidermis
Excoriation	Linear break in the skin surface caused by scratching covered with blood or crusts, usually in response to itching
Lichenification	Leathery induration, thickening and increased wrinkles of the skin caused by repeated scratching
Macule	Skin area of flat colour change. Some centers use the term macule for small lesions (<1.5cm) and patch for larger areas
Nodule	Elevated circumscribed tissue growth in or under the skin (≥ 0.5cm)
Papule	Small (<0.5cm) raised circumscribed growth protruding above the skin
Patch	Large flat area of colour change
Petechia	Haemorrhagic punctuate spot measuring 1–2 mm in diameter
Plaque	Elevated plateau-like lesion, usually more than 2 cm in diameter
Pustule	Circumscribed elevated lesion containing pus
Ulceration	Full-thickness loss of the epidermis
Vesicle	Small (< 5 mm in diameter) elevated circumscribed lesion filled with clear fluid
Wheal	Transient itching compressible dermal oedema of variable size and form, red or white in colour
Xerosis	Dry skin because of lack of skin hydratation. Also called Sebostasis.

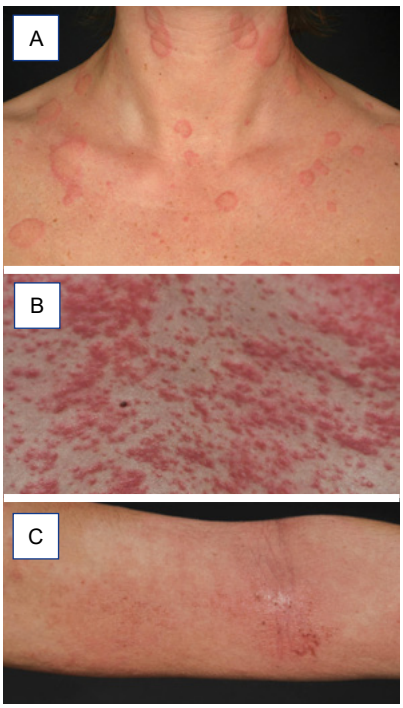

Figure 1 Main morphological features of pruritic skin lesions of allergic diseases. A. Urticaria with disseminated sharply demarcated oedematous whitish-red wheals lasting < 24 hours each, which might form different shapes (e.g. annular, geographical). B. Sharply demarcated, potentially confluent suddenly erupting red macules and papules, which resolve after about a week are the mainstay of a maculopapular exanthema. C. In eczema, the skin is diffusely involved, typically without a distinct border, but with induration, xerosis and fine scales, crusts, excoriations, lichenification

chronic lesions) (Figure 1C). As the differential diagnosis of allergic skin diseases is not always easy, identification of skin lesions, morphology, distribution patterns, and the use of dermatological terms and descriptions appropriately are needed to make the correct diagnosis, aided by history, histopathology and/or allergy tests.

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TABLE 2

Dermatological terms for morphological descriptions in allergic skin diseases	
Confluent	Lesions, which are coming together merging into a continuous shape
Desquamation	Scaling of upper epidermal layers following skin inflammation
Disseminated	Disease extent is with widespread lesions and different skin regions involved
Erythema	A large area arising from vascular dilation causing redness
Erythroderma	Reddening of >95% of body surface area of the skin
Enanthem	Red acutely erupting small macules on the mucous membranes
Exanthem	Acutely erupting, widespread distribution of multiple small, round to oval erythematous macules and/or papules, which may confluence. Non-standardised terms sometimes used for describing features of maculopapular exanthems resembling specific diseases are e.g. acneinform, lichenoid, morbilliform, pustular, urticarial, vesicular
Flexural	Arising on the body folds (intertriginous) and inner surfaces of limbs
Generalised	Disease extent is with widespread lesions where no major regions of skin are exempt
Induration	Thickened dermis usually implying underlying cellular infiltrate
Localised	Lesions are limited to a certain area of the body
Purpura	Multiple petechiae by extravasation of red blood cells resulting in red discoloration of the skin or mucous membranes
Rash	Unspecific term for a sudden cutaneous eruption regardless of etiology also including urticaria
Target lesion	Concentric rings with different grades of erythema and edema resembling targets in Erythema multiforme. They consist of three concentric zones with central epidermal damage, oedematous intermediate and outer erythema.
Violaceous	Skin change coloured violet, typically suggests deep inflammation

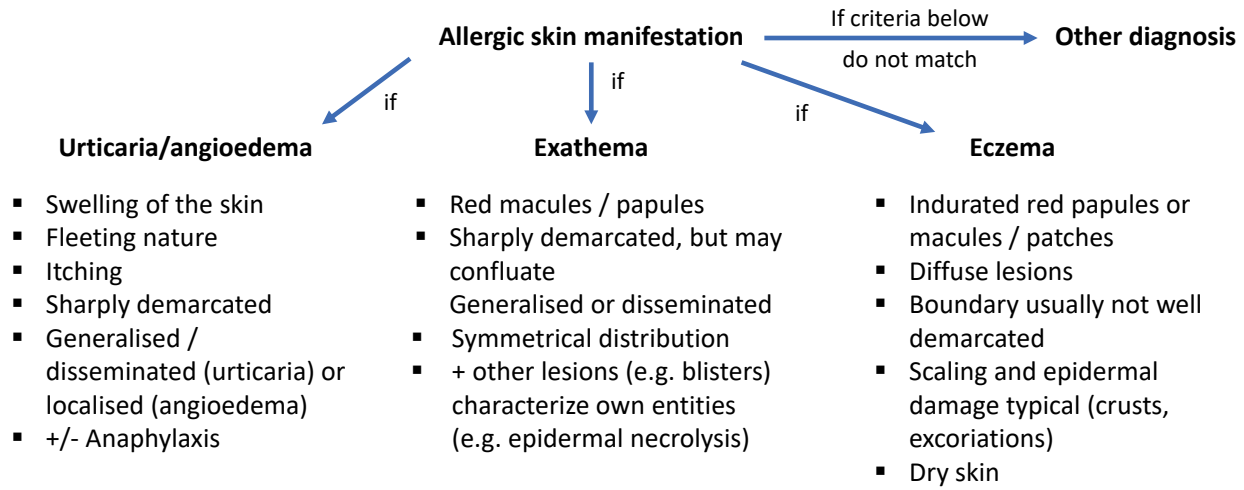

Figure 2 Morphological differential diagnosis between the most important entities in allergic diseases of the skin

2 HISTOPATHOLOGY

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KEY MESSAGES

- Histologically, distinction between allergic and irritant contact dermatitis is almost impossible
- Also histologically, it may be impossible to differentiate viral exanthem whereas graft-versus-host-reactions usually show more apoptotic keratinocytes and involvement of adnexal structures
- In patients with an urticarial rash unresponsive to standard treatments for urticaria, skin biopsies are useful to differentiate urticaria from neutrophilic urticarial dermatosis, a reaction pattern seen in autoinflammatory disorders, lupus and some other inflammatory disorders

Inflammatory dermatoses are usually diagnosed clinically. In the context of skin allergies, the histopathological pictures of eczema, maculopapular drug reactions, urticaria and mastocytosis will be discussed here.

Histologically, distinction between allergic and irritant contact dermatitis is almost impossible. Both, acute and subacute eczema show spongiosis (Figure 1A and B) (broadened intercellular spaces between keratinocytes) histologically, with variable intraepidermal vesiculation and parakeratosis with inclusion of serum. There is a superficial perivascular lymphocytic infiltrate with variable eosinophils.

In chronic eczema, there is an irregular or "psoriasiform" hyperplastic epidermis with parakeratosis and a superficial perivascular lymphocytic infiltrate. As with all inflammatory dermatoses, a PAS (*Periodic Acid-Schiff*) stain should be done, to not miss dermatophytes. However, this stain does not replace mycological examination of scales.

Clinically, the differential diagnosis of maculopapular exanthems includes drug reactions, viral exanthems and early graft-versus-host reaction.

Histologically, maculopapular drug reactions show a superficial and sometimes deep perivascular lymphocytic infiltrate with few admixed neutrophils and eosinophils (Figure 2A and B). Depending on the stage there is ortho- or slight parakeratosis. The lower epidermis is slightly spongiotic with discrete vacuolar change and few apoptotic keratinocytes along the dermoepidermal junction. Neutrophils can be detected in the dilated vessels. Also histologically, it may be impossible to differentiate viral exanthem whereas graft-versus-host-reactions usually show more apoptotic keratinocytes and involvement of adnexal structures.

In urticaria, the epidermis is unchanged. Cell type and density of the dermal infiltrate vary depending on the age of the lesion biopsied and causal stimulus (Figure 3A and B). Usually, the infiltrate is seen in the upper dermis and variably extends into the dermis and sometimes also subcutis. The infiltrate consists of perivascular lymphocytes, interstitial eosinophils, neutrophils and mast cells. A neutrophil rich infiltrate is more typical in early biopsied lesions and in pressure induced urticaria. Leukocytoclasia can be observed and should not be confused with leukocytoclastic vasculitis as typical fibrin deposits are missing.

In neutrophilic urticarial dermatosis, an urticarial reaction pat-

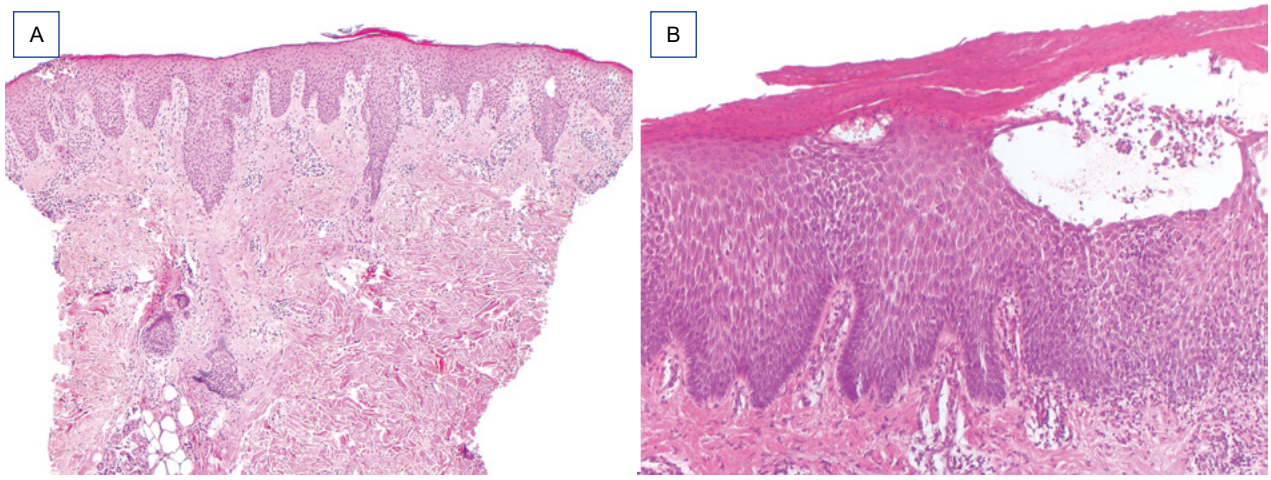

Figure 1 Spongiotic dermatitis. Subacute eczema: spongiotic and psoriasiform epidermis with parakeratosis, and superficial perivascular infiltrate (A). The intercellular edema in spongiosis causes widening of intercellular spaces and spongioform vesiculation beneath a thickened and parakeratotic stratum corneum. There is exocytosis of some lymphocytes into the spongiotic epidermis (B)

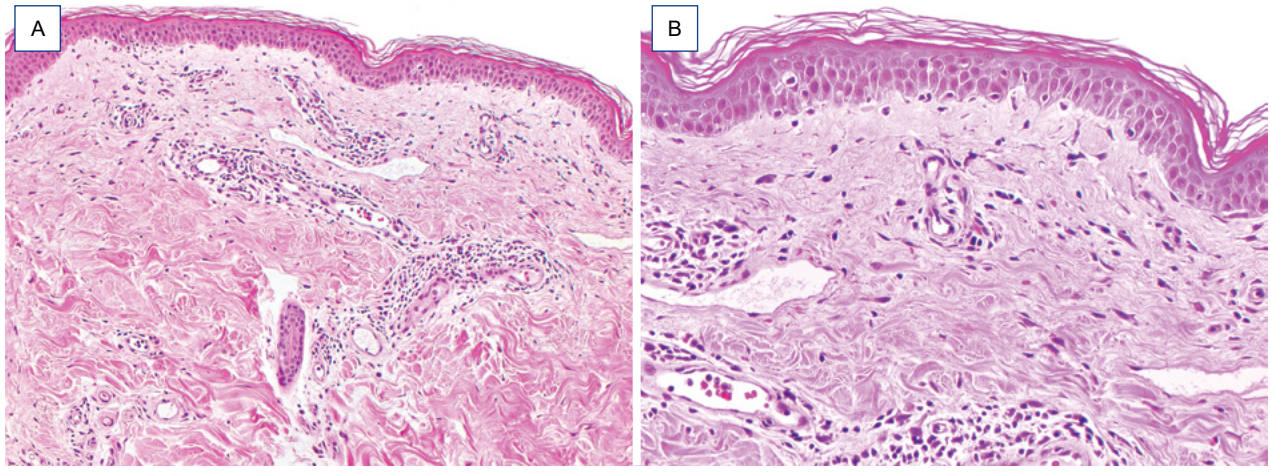

Figure 2 Maculopapular drug eruption. There is slight spongiosis of the epidermis with subtle vacuolar change in the dermoepidermal junction (A). The superficial perivascular infiltrate consists of lymphocytes with few admixed neutrophils and eosinophils. Neutrophils are seen within dilated blood vessels (B)

tern seen in autoinflammatory disorders but also lupus erythematosus, Sjögren's syndrome and other inflammatory disorders, a perivascular and interstitial neutrophilic infiltrate with variable leukocytoclasia but no vasculitis is observed. Typically, neutrophils might be found within the epidermis and sweat gland epithelia, a so-called neutrophilic epitheliotropism.

Histologically, maculopapular cutaneous mastocytosis belongs to the group of invisible dermatoses. To identify mast cells, a Giemsa (or toluidine) stain should be done as the granules within mast cells show a typical metachromatic behaviour. Nowadays, many centers do apply a tryptase and or anti-CD117 stain. Depending on the form of mastocytosis in the skin there is a variably dense infiltrate of oval to spindled mast cells in the dermis with few admixed

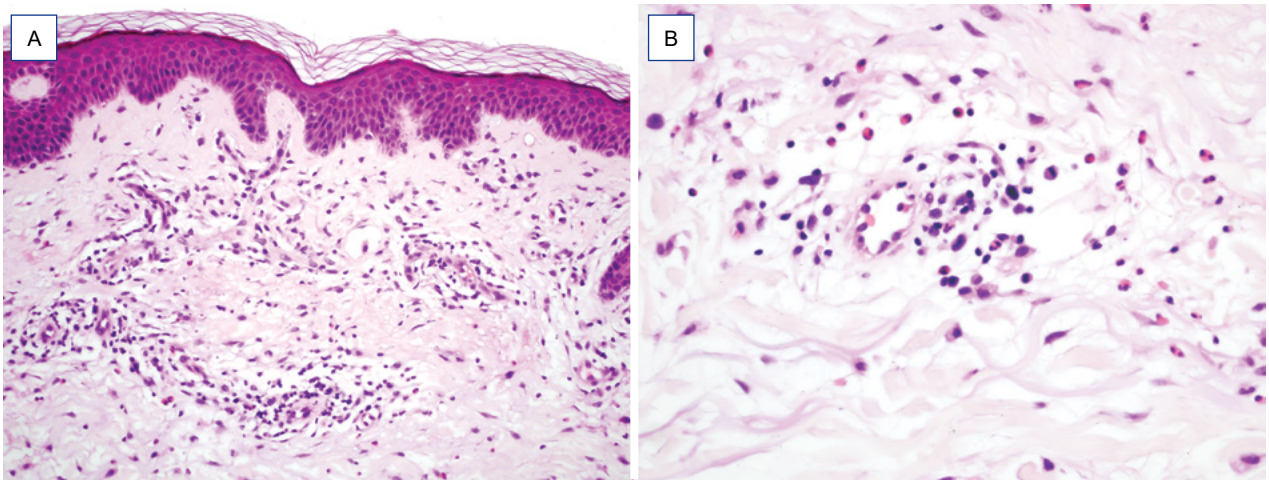

Figure 3 Urticaria. The epidermis is unchanged with basket-weave stratum corneum (A). There is a superficial perivascular lymphocytic infiltrate with interstitial eosinophils and few mast cells (A, B). The blood vessels are slightly dilated and the vessel walls are intact. Within the lumen there are few neutrophils (B)

eosinophils and basal hyperpigmentation of the epidermis. There is no consensus on the density of mast cell infiltrate in the skin necessary for the diagnosis of maculopapular type of mastocytosis.

In summary, skin histology of dermatological diseases in the context of allergy can show different histological patterns that might be specific or unspecific. Therefore, a histological report should always be correlated with the clinical context in order to support a clinical suspicion of eczema, viral/drug exanthema, urticaria or mastocytosis in the skin.

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3 DERMATOLOGICAL DIFFERENTIAL DIAGNOSIS OF ALLERGIC SKIN REACTIONS

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The skin presents a wide and diverse repertoire of reaction patterns to exogenous and endogenous events that may confound diagnosis of allergic skin reactions. The most common allergic skin reactions are allergic contact dermatitis or acute urticaria. The differential diagnosis includes immunological conditions (e.g. autoimmune) or infections (viral, bacterial or fungal). Allergy is defined clinically as a bad clinical reaction to an exogenous trigger involving the immune system. The Gel and Coombs classification of hypersensitivity reactions subdivides pathogenesis into Type I ('anaphylactic' or immediate, due to specific IgE/allergen activation of mast cells or basophils), Type II (antigen-antibody dependent cytotoxicity with or without complement activation), Type III (soluble immune complexes causing local inflammation) and Type IV (delayed inflammation resulting from antigen presentation to sensitized T lymphocytes). Fortunately, allergic reactions in the skin are predominantly Type I or Type IV and their clinical presentations are usually distinctive. Drug reactions are more complex and are discussed elsewhere.

KEY MESSAGES

- Allergy in the skin is mainly Type I (immediate 'anaphylactic' hypersensitivity) or Type IV (delayed hypersensitivity)
- Dermatitis and acute urticaria may be allergic but not chronic urticaria
- Allergic contact dermatitis is confirmed by patch testing. Immediate allergic reactions are confirmed by measurement of specific IgE or skin prick testing
- The clinical presentation and dermatological differential diagnosis depends on the affected body site

Clinical diagnosis depends on the history and examination (Table 1) of the physical signs that may result from acute skin inflammation. Acute allergic dermatitis typically develops hours, or even a day, after sufficient skin contact with the allergen, to allow penetration through the stratum corneum. Acute urticaria, on the other hand, usually presents within an hour, or even minutes, of ingestion or contact with an allergen to which the body is pre-sensitized, although many cases do not appear to have an allergic aetiology after full evaluation. Chronic urticaria also involves mast cell activation but allergy is not the cause. Immediate hypersensitivity may be relevant in atopic dermatitis in the context of protein contact dermatitis and the head and neck pattern of eczema in adults with IgE sensitization to pityrosporum yeasts.

The differential diagnosis and presentation of cutaneous allergy may be influenced by body site: for instance, dermatoses presenting with periorbital involvement include angioedema (Figure 1), dermatitis (Figure 2) and a spectrum of dermatological diseases that may require skin biopsy for clinicopathological correlation (Table 2).

There must be a history of prior exposure to an allergen to suspect allergy is a possible cause of skin disease. The appropriate investigation for allergic contact dermatitis is patch testing. Suspected allergic urticaria should be inves-

TABLE 1

Clinical diagnosis depends on history and examination features						
	Itch	Pain	Fever	Duration	Pattern	Residue
Dermatitis	++	-	-	Days or weeks	Uni- or bilateral	Scaling, pigmentary change
Urticaria	+++	-	-	Hours	Bilateral	-
Angioedema without wheals	+/-	+/-	-	Up to days	Uni-or bilateral	-
Urticarial vasculitis	+	Burning	+/-	Days	Bilateral	Bruising
Autoinflammatory syndromes	+/-	+/-	+	Hours	Bilateral	-
Erysipelas	-	+++	++	Days	Unilateral	-
Viral exanthems	+/-	+/-	+	Days	Bilateral	-
Fungal infections	+/-	-	-	Weeks	Uni- or bilateral	Pigmentary change

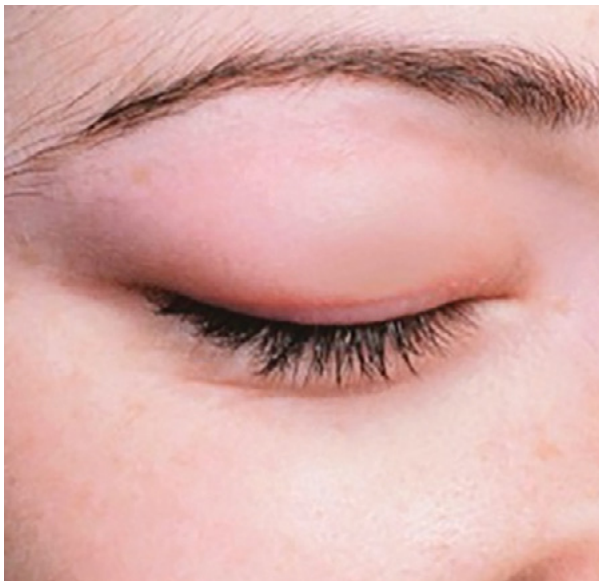

Figure 1 Angioedema of the eyelids showing marked pale pink subcutaneous oedema without epidermal change

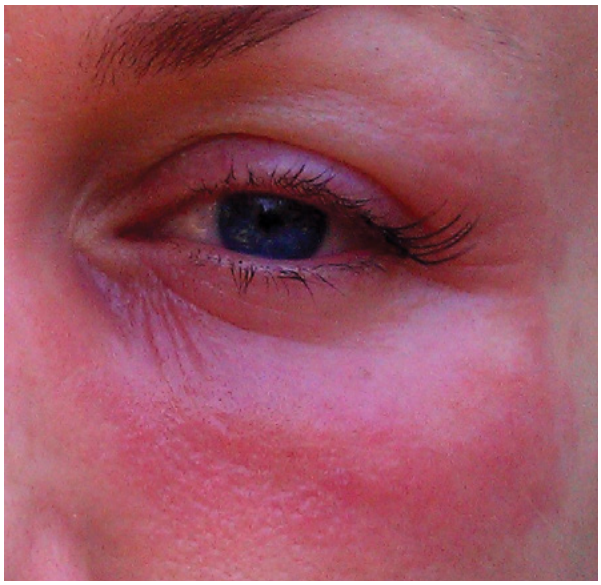

Figure 2 Acute allergic dermatitis of the eyelids showing deep redness, mild oedema and superficial skin creasing

tigated for specific IgE in blood (e.g. ImmunoCAP™, Phadia) or skin prick testing. Open or closed 30 minute patch testing may be needed to confirm allergic (immunological) contact urticaria. Provocation testing may occasionally be appropriate but usually in the context of proving a negative rather than confirming an allergy in real world practice.

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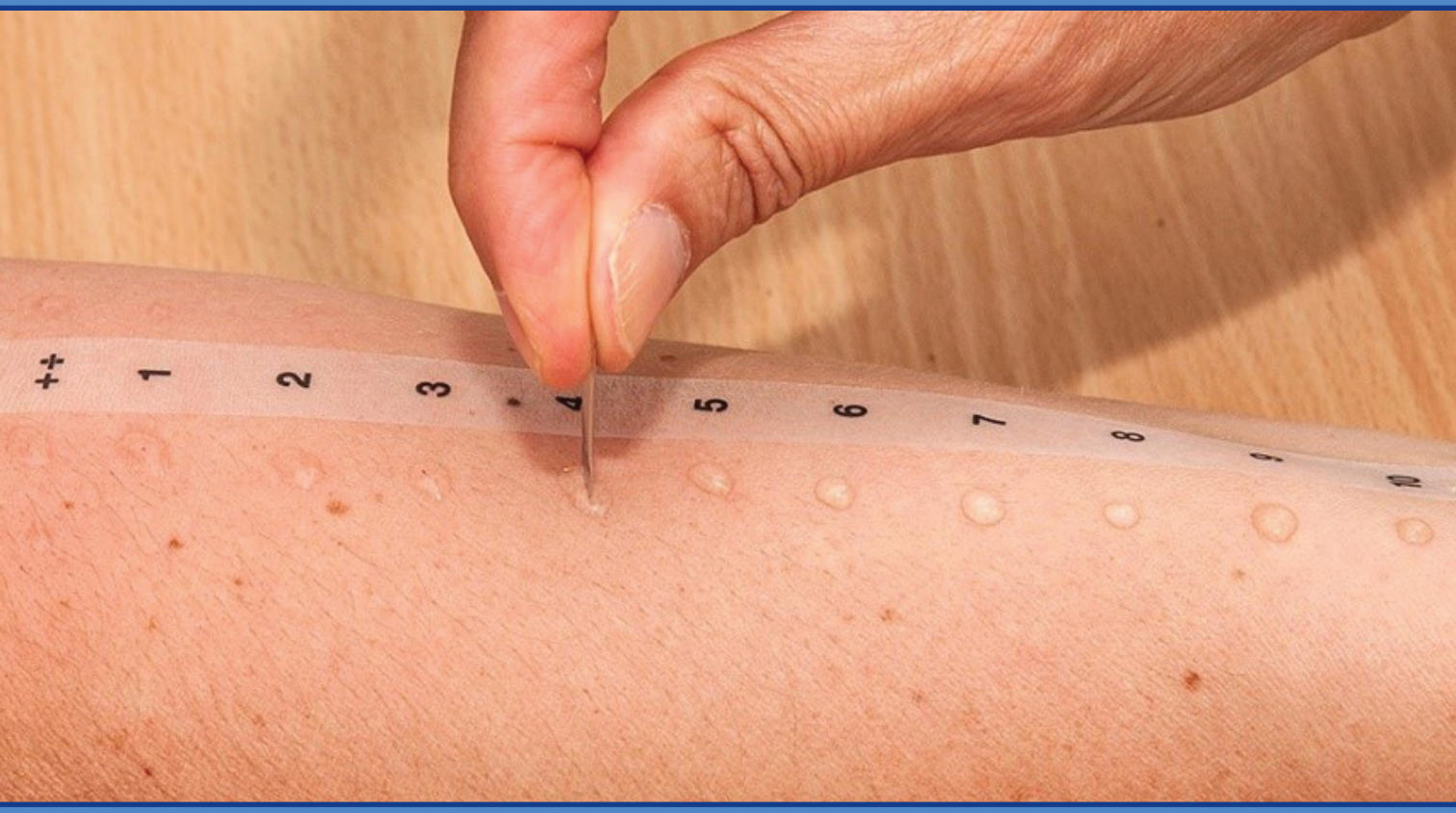
TABLE 2

Differential diagnosis of periorbital swellings

	Subtype	Other features	Allergic?
Angioedema	Histaminergic	May be a feature of urticaria or anaphylaxis	Possible in the context of acute urticaria, contact urticaria and anaphylaxis
	Bradykininergic	Hereditary angioedema (HAE) and angiotensin converting enzyme (ACE) inhibitor induced	No
Dermatitis	Contact allergic	Wide range of potential causes including cosmetics and preservatives	Yes
	Seborrhoeic	Secondary to pityrosporum yeasts	No
	Atopic	May occur with severe allergic conjunctivitis	Yes
Dermatomyositis	Autoimmune or paraneoplastic	With or without myositis	No
Rosacea	Lymphoedematous variant	Also known as Morbihan's disease	No

Section D



DIAGNOSIS

* Allergy tests on the skin: Skin prick test
* Allergy tests on the skin: Drug intradermal tests
* Allergy tests on the skin: Patch test
* Allergy tests on the skin: Atopy patch test
* Allergy tests on the skin: The repeated open application test (ROAT)
* Allergy tests on the skin: Skin Application Food Test (SAFT) and food contact provocation test
* Allergy tests on the skin: Use of physical provocation tests on the skin
* Molecular diagnosis for skin allergy

1a ALLERGY TESTS ON THE SKIN: SKIN PRICK TEST

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The skin prick test is used in the diagnosis of immediate type hypersensitivity (IgE mediated allergy) to inhalant allergens, foods, insect venoms, occupational allergens and drugs in patients of all ages. It is easy to perform and very reproducible when performed by trained personnel; it carries very low risk and provides an immediate answer in most cases. A positive test confirms sensitization, but should always be interpreted in the light of a clinical history of relevant symptoms on exposure to the allergen.

KEY MESSAGES

- The skin prick test is the most commonly used test in allergy investigation
- The skin prick test is easy to perform and very reproducible
- The skin prick test can be performed with most allergens such as allergen extracts, fresh foods and drugs

METHOD FOR SKIN PRICK TESTING

Prior to skin prick testing with allergens, skin reactivity should be tested by performing a positive control with e.g. histamine, and dermographism should be excluded by performing a negative control with normal saline. Attempts have been made to standardise methods. The most common method is to place drops of different test solutions on the volar surface of the forearm and to puncture the skin through the drop with a fresh lancet, or other locally available preferred device, for each drop (Figure 1). Then excess solution is blotted off with a serviette to avoid cross contamination of test sites, and the test is read 15 minutes later.

INTERPRETATION OF SKIN PRICK TESTING

The appearance of a wheal with a diameter of ≥ 3 mm in the presence of a flare and itch is considered positive. The result of a skin prick test may depend on patient factors such as skin reactivity, the tester, e.g. differences in pressure applied, the device used, and the allergen. False positive testing may occur in patients with urticaria and dermographism and false negative testing may occur as a result of treatment with antihistamines or other drugs with antihistaminergic effect, such as antidepressants. Supplementary tests such as specific IgE, allergen component diagnostics, other *in vitro* tests or even provocation testing should be performed if test results are not considered conclusive. Repeating testing on a different date may also provide different results.

ALLERGENS

Some allergen extracts used for prick test are commercially available standardized test extracts, as is the case for insect venom allergens (bee/wasp), and inhalant allergens which in many countries comprise pollens, animal dander, house dust mite and moulds. Local variations may reflect common

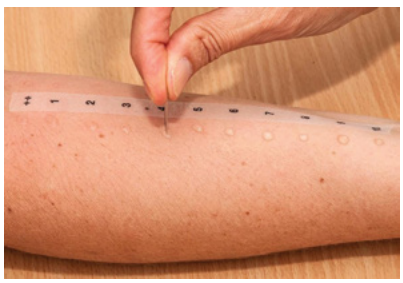

Figure 1 Skin prick testing performed on the volar forearm

Figure 2 Example of panel for food allergy testing comprising codfish, prawn, hazelnut, peanut, celeriac and apple

allergens in different regions of the world.

Suspected food allergens are often tested naive with a prick-to-prick test where the lancet is pricked into a raw food and then pricked into the patient's skin. Many centres have panels with the most common food allergens (Figure 2) and more specific panels for e.g. cereals and nuts.

Skin prick test can also be performed with drugs, ideally with parenteral or other liquid formulations of suspected drugs, but creams, gels and in some cases solid material can be tested by the prick-to-prick method. Negative and/or doubtful results in drug allergy testing could be supplemented by intradermal testing or *in vitro* testing. Standardised concentrations should be used to minimise risk of false positive testing.

The risk of systemic reactions to skin prick test is very low, but have been described rarely mainly in food and drug allergy testing. Skin prick testing should therefore only be performed in settings where anaphylaxis can be diagnosed and treated according to guidelines.

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1b ALLERGY TESTS ON THE SKIN: DRUG INTRADERMAL TESTS

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KEY MESSAGES

- Drug intradermal tests are the most sensitive drug skin tests but also those which have the highest risk of inducing a systemic reaction
- They have to be done in injecting a known volume of 0.02 ml
- The results of IDT have to be read carefully after 20 mns
- In investigating delayed hypersensitivity to drugs, delayed readings of IDT after 1 or 2 days are necessary

Allergy skin testing is essential for the correct diagnosis of immediate and delayed drug hypersensitivity. It is also used to identify alternative drugs for patients with positive skin or provocation tests with suspected drugs. The intradermal test (IDT) is the most sensitive skin test and may be used when soluble forms of the drugs are available. This chapter concerns IDT in drug allergy, but IDT are also very useful for testing allergies to hymenoptera venoms.

A position paper providing guidelines on drug concentrations for skin testing was published in 2013. In order to avoid high differences in results related to non-standardized methods, the European Network in Drug Allergy (ENDA), the Drug Allergy Interest Group of EAACI recommends a strict methodology to follow for performing drug IDT.

At the moment, we did not know if there is any influence of the injection sites which are the lateral aspect of the upper arm, or the flexor aspect of the forearm or the back.

Using a fixed volume of an IDT drug solution of known concentration means to inject a known and fixed quantity of the tested drug. In case of flare-up, it is very important to know the exact amount of the drug administered.

We propose the ten following recommendations for performing drug IDT:

1. IDT must be performed, following negative prick tests, using pharmaceutical grade human drugs in injectable form. IDTs are done with increasing concentrations of the drug tested. In case of anaphylactic shock, particularly with betalactam antibiotics, IDTs are started at very low concentrations. In such cases, prick tests done before have also to be performed with progressively increased concentrations. Using crushed pills, even after filtration is not recommended. IDT is contraindicated in severe cutaneous adverse drug reactions such as toxic epidermal necrolysis, and also with the highly suspected drugs in acute generalized exanthematous pustulosis (AGEP) or drug reaction with eosinophilia and systemic symptoms (DRESS). In DRESS and AGEP, IDT with drugs having a low imputability or replacement drugs having a low risk of cross reactions with the highly suspected drugs have to be discussed.
2. We recommend to use a tuberculin syringe of preferably 0.5 ml or if not available, 1 ml volume, with a needle gauge of 25, 27 or 30G. The needle used for dilution or a new needle can be used for test IDT. Syringe with flat end plunger are better than tapered end to help to measure the volume of

Figure 1 Tuberculin syringe with 25G needle and flat end plunger drawn up with 0.02 ml solution

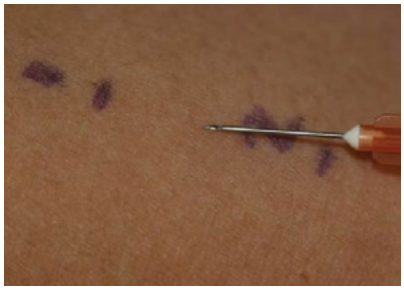

Figure 2 Inject with the bevel of the needle facing upwards

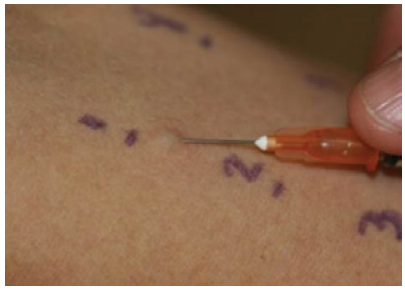

Figure 3 Pierce skin tangentially in the upper dermis (at about 10° angle to the skin surface) and inject the whole volume (0.02 ml)

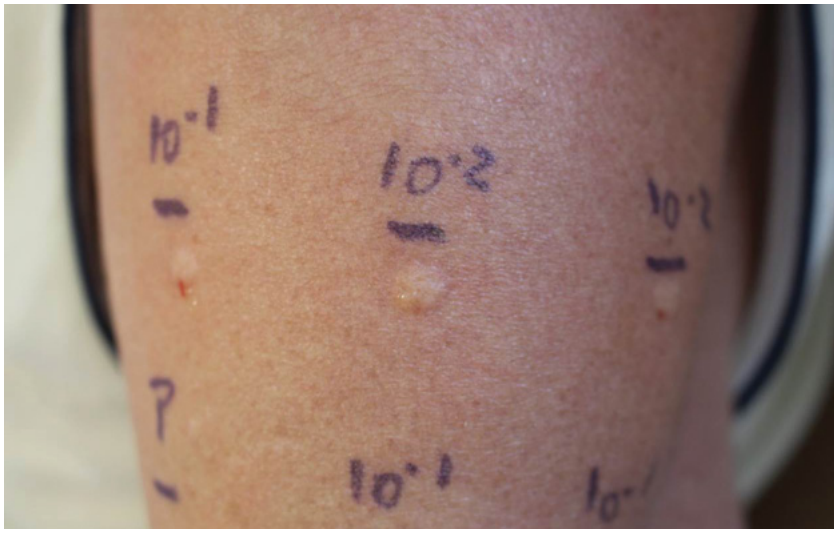

Figure 4 The injection wheal has a specific feature in "peau d'orange"

test solution drawn into the syringe.

3. The injection technique has to be strictly followed. You have to adopt sterile techniques. You fill the syringe with test solution, then you can change the needle if not fixed. Tap the barrel of syringe makes air bubble rise to needle end of syringe. You have to expel air bubble and excess volume pushing plunger to 0.02 ml mark on barrel (Figure 1). That is to say, you only keep 0.02 ml volume into the syringe. With the bevel of the needle facing upwards (Figure 2), you pierce skin tangentially in the upper dermis (at about 10° angle to the skin surface) (Figure 3). Then to avoid painful injection, you slowly inject the measured volume intradermally. You get a specific feature of a wheal in "peau d'orange" (Figure 4).
4. Respecting these procedures, usually you get a wheal of 4.5 to 5.5 mm in diameter. If you do not get clear wheal forms, repeat injection of a controlled volume of 0.02 ml.
5. You have to record all injected solutions, batch number and map of injection sites. You have to draw around and/or measure the diameter of the immediate injection wheal (Wi). If you surround the wheal with ink, always measure the inner diameter.
6. If the wheal is not round, you measure the length (L), then the width (w) taken perpendicularly, in the middle of the axis length. The Wi will be the result of (L+w)/2.
7. You have to read the IDT after 20 minutes. You measure the wheal called W_{20} and the surrounding erythema called E_{20}.

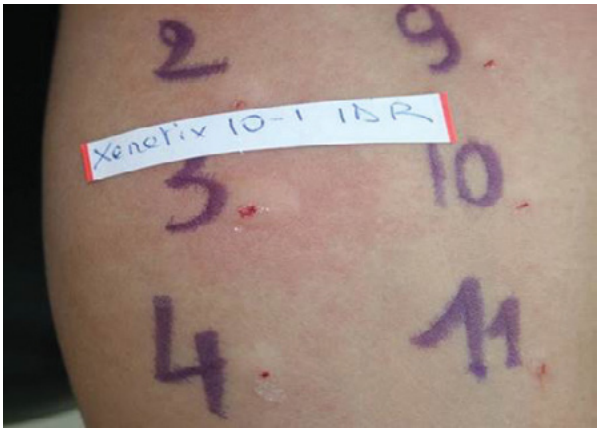

Figure 5 An immediate positive result of an intradermal test with iobitridol, 20 minutes after the intradermal injection (Position 3). The other IDT have negative results on sites 2, 4, 9, 10 and 11. Results are positive when you get a wheal (with a diameter equal or more than the initial wheal) and a surrounding erythema

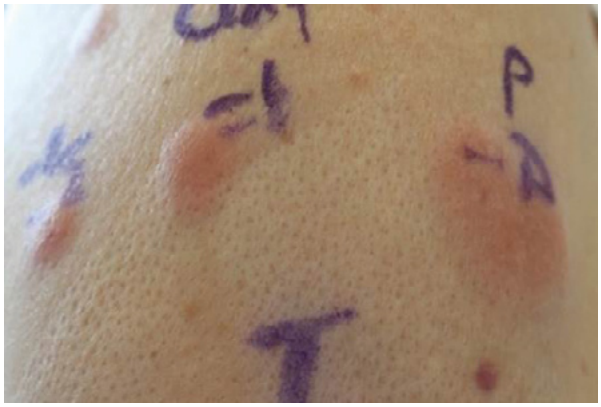

Figure 6 Positive results on intradermal tests done with betalactam antibiotics read after 48h, with an erythematous infiltrated reaction

If the wheal is not round, you measure L, then the w taken perpendicularly, in the middle of the axis length, and the W_{20} will be the result of (L+w)/2.

8. In patient records and publications, IDT results must be recorded as follows: Wi, W_{20} and E_{20}.
9. In literature, there are different criteria for positive results. We recommend using the EAACI criteria (2): at 20 min the IDT is considered positive only if there is a wheal, $W_{20} \geq Wi + 3$ mm and a surrounding erythema (E_{20}) (Figure 5). A W_{20} without any surrounding erythema can occur *e.g.* with iodinated radiocontrast media tested at high concentrations, it is not a positive result!
10. Delayed reactions are read at 24 h, 48 h or later (the time interval has to be specified). IDT are considered positive when there is an erythematous induration or swelling at the injection site (Figure 6). With corticosteroids delayed readings have to be done after 1 week, with heparins they have to be performed after 72 or 96 h, or even later, as very late reactions may be observed.

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1c ALLERGY TESTS ON THE SKIN: PATCH TEST

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KEY MESSAGES

- Patch testing is done in patients, where contact allergy or delayed drug allergy is suspected or needs to be excluded
- It is advised to consult guidelines prior to patch testing
- Testing with substances outside the baseline series is a specialist task, as these often are less standardized and require expert judgement
- A positive patch test – from a technically well-conducted test- is a sign of sensitization
- Allergic contact dermatitis requires a positive patch test to an allergen and a present exposure to that allergen, which may at least partly explain the dermatitis

PATCH TESTING

Patch testing is the standard method for diagnosing contact allergy (sensitization) and a step in the diagnosis of allergic contact dermatitis. It is an in-vivo test, where the patient is epicutaneously exposed to small amounts of the suspected allergen(s) under controlled circumstances, followed by readings of the clinical response over several days. The patch test is performed according to international guidelines and should be performed in all patients in whom contact allergy is suspected or needs to be excluded. In addition, patch tests are done for the diagnosis of drug exanthems. There are conditions where a test should be postponed, e.g. in case of severe or generalized active dermatitis or exanthem, which may influence the outcome of the test.

ALLERGENS

Contact and delayed drug allergens are mostly low-molecular weight chemicals, i.e. haptens. A standardized set of the most frequent allergens are compiled in the baseline series, relevant to the geographical region. In Europe the baseline series contains around 30 individual allergens or mixtures of allergens. In addition to the baseline series allergens of relevance to the patient's exposures in their home environment and at the workplace are added to the test. Around 600 allergens are commercially available. However, many more allergens exist, and the final test set of allergens depend on a thorough and individual exposure assessment.

PATCH TEST SYSTEMS

Two principally different systems exist. A ready to use system, with pre-loaded chambers of a limited number of allergens or systems where the investigator loads the chambers with the allergens in solutions of water, alcohol or petrolatum. These two main systems are methodologically equally valid.

APPLICATION AND READING

There are many technical issues to consider before and during patch testing to ensure a valid result (Table 1), therefore it is advised to consult guidelines prior to patch testing. Patches are applied on the upper back and left in place for 2 days (Figure 1). At least two readings are recommended day 3 or 4 and day 7. If no late reading is done 20% of allergies will be overlooked.

Readings are made based on morphological criteria (Table 2), so that a minimum requirement for a positive test is homogeneous erythema and infiltration of the whole test area (Figure 2). Testing with substances outside the base-

TABLE 1

Some key technical issues in patch testing
The recommended baseline series for the geographical region is usually the starting point for patch testing
Additional allergens for patch testing are selected based on an exposure analysis
Do not test products with an unknown content, pH <4>9 or in case any ingredient exceeds the concentration which is recommended for patch testing.
Patch test materials should be stored at 4C and protected from light.
Volatile materials should be dosed in the chambers immediately prior to application of test.
Chambers should be dosed correctly, as under-or overfilling may cause a risk of false negative or positive reactions and in case of potent allergens a risk of sensitization. The dose depends on the chamber size used.
The upper back is the preferred site for patch testing
Occlusion time is 2 days
At least 2 reading are required, but ideally 3 times: D2, D3 or D4 and D7
The patch test is scored according to morphology
A positive patch test is defined as a reaction that fulfills the criteria of at least 1+ reaction

TABLE 2

Reading scale for patch test reactions (see Johansen JD et al.)		
Symbol	**Morphology**	**Assessment**
-	No reaction	Negative
?+	Faint erythema	Doubtful
+	Erythema, infiltration in the whole test area	Positive (Figure 2)
++	As above and vesicles	Positive
+++	As above and coalescing vesicles	Positive
IR	Various: soap effect, necrosis, bulla	Irritant = negative

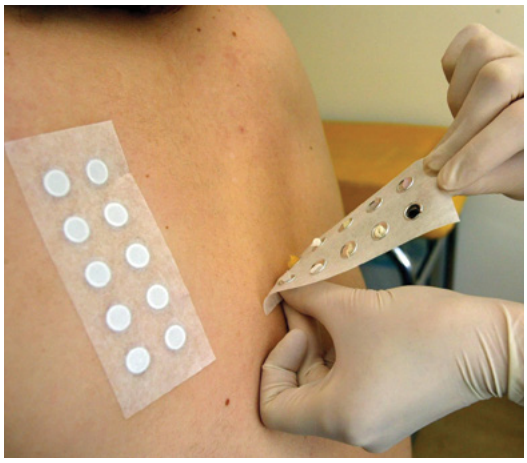

Figure 1 Application of patch test

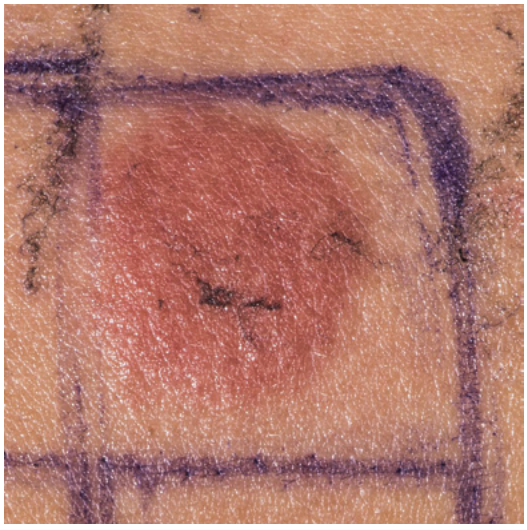

Figure 2 A positive patch test: a + reaction

line series is a specialist task, as these often are less standardized and require expert judgement.

INTERPRETATION

Sometimes to correctly interpret a patch test reaction reapplication will have to be done, testing with serial dilutions of the allergens or use tests. A positive test is a sign that sensitization has occurred, while the diagnosis of allergic contact dermatitis requires a current (or past) exposure to the allergen, which may at least partly explain the dermatitis.

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1d ALLERGY TESTS ON THE SKIN: ATOPY PATCH TEST

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KEY MESSAGES

- APT is indicated in patients with eczema with suspicion of aeroallergen symptoms without proof of positive specific IgE and/or a positive skin prick test, in patients with severe and/or persistent AD with unknown trigger factors or multiple IgE sensitizations without proven clinical relevance
- *D. pter.* is the most frequent allergen eliciting positive APT reactions, APT performed with food proteins can detect delayed eczematous reactions to food
- The characterisation of a patient subgroup with relevant aeroallergen IgE-mediated allergy may lead to more efficient avoidance and specific immunotherapy strategies in the management of AD
- The role for IgE in the reaction mechanism of APT is corroborated, since in most APT-positive patients elevated specific IgE was found compared to those with negative APT. However, high allergen-specific IgE in serum is not a prerequisite for a positive APT
- A cellular mechanism without direct involvement of IgE may be hypothesized to explain the clear-cut positive APT reactions in a subgroup of AD patients
- Practical aspects: APT is possible on non abraded skin without manipulation of the skin barrier function. Allergen lyophilisate in petrolatum is the preferred preparation. Allergen concentrations higher than in most skin prick test solutions are necessary for APT (but lower doses can be used in children)

SKIN TESTING IN PATIENTS WITH ATOPIC DERMATITIS

While the pathophysiology of IgE-mediated allergic rhinoconjunctivitis and bronchial asthma is well established, the role of allergy in atopic dermatitis (AD) is still controversial. By a technique called atopy patch test (APT), aeroallergens like house dust mite, animal dander or pollen were proven as relevant trigger factors in a subgroup of patients with AD. The APT is an epicutaneous patch test with allergens known to elicit IgE-mediated reactions, and the evaluation of eczematous skin reactions (Figure 1, 2). Aeroallergen APT was frequently used in clinical practice in the EU, APT preparations are now used on an individual basis due to regulations and availability. In a series of single and multicenter studies, a method was standardized and compared to other diagnostic techniques (specific IgE, skin prick test) in AD patients (Table 1). APT is read according to European Task Force on Atopic Dermatitis (ETFAD) guidelines (Table 2, for review see 3). With regard to clinical history, the most specific results were obtained with the APT (allergen-dependent 69-92%), while sensitivity was higher for skin prick test (69-82%) and specific IgE (65-94%) (Table 3).

According to the results of Langeveld-Wildschut et al., the positive APT reaction requires the presence of epidermal IgE+ CD1a+ cells. In biopsies of pollen-grain induced APT, the immune response has been characterised as a rapid and biphasic eczematous reaction. T-cells showed a characteristic TH2 secretion pattern initially

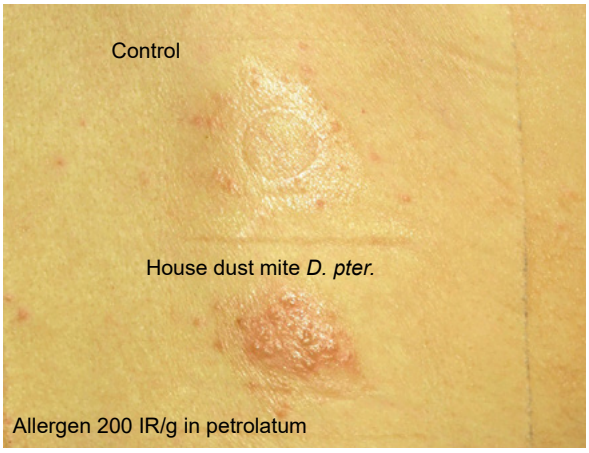

Figure 1 APT with house dust mite D. pter. in a patient with atopic dermatitis (AD). Eczematous reaction after 48 hours

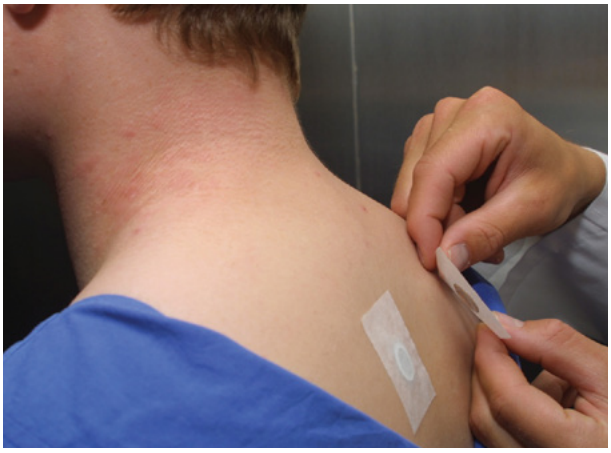

Figure 2 APT in a patient with AD

TABLE 1

Clinical covariates of the APT in two multicenter studies with different allergen standardisation*

	Skin prick		sIgE		APT		History	
	A	B	A	B	A	B	A	B
D. pter.	59%	56%	56%	56%	34%	39%	52%	34%
Cat dander	54%	44%	49%	46%	12%	10%	23%	30%
Grass pollen	65%	57%	75%	59%	18%	15%	33%	31%
Birch pollen	65%	49%	65%	53%	11%	17%	13%	20%

** A: German multicenter (1) (7 centres, N = 253 adults, dose-finding 3000-10000 PNU/g); B: European multicenter (2) (6 countries, 12 centres, N = 314, 200 IR/g). Percentages of clear-cut positive test results are given*

TABLE 2

ETFAD reading of APT (3)	
-	negative
?	only erythema, questionable
+	erythema, infiltration
++	erythema, few papules
+++	erythema, many or spreading papules
++++	erythema, vesicles

TABLE 3

Sensitivity and specificity of different diagnostic methods in two studies with patients with AD. Better results are obtained with a seasonal allergen: grass pollen (1,3)

Test	Sensitivity*	Specificity*
Single center study n=79, allergen: grass pollen		
Skin prick	100%	33%
Specific IgE	92%	33%
APT	**75%**	**84%**
APT Multicenter study n=253, 3 allergens		
Skin prick	69-82%	44-53%
Specific IgE	65-94%	42-64%
APT	**42-56%**	**69-92%**

**referring to predictive history of eczema exacerbations in pollen season or in direct contact with allergen, excluding questionable cases, ranges depending on allergen (multicenter trial)*

(24h) and an IgE and IL-5 predomination, whereas in the late phase (96h) a TH1 pattern accompanied by an IFN-γ predominance was observed. This same pattern is also found in chronic lesions of atopic eczema. Furthermore, in a recent study hypoallergenic rBet v1 fragments were used to demonstrate that the reactions are often non-IgE mediated.

Food APT is still an experimental method, but the available standardized food challenge protocols (gold standard) allowed the evaluation of the clinical relevance of food APT reactions. Often, native food like hen's egg, wheat flour, cow's milk or soy products were applied in 12 mm aluminium test chambers for 24 or 48 hours on the patient's skin (problem: frequent irritation). More recently, food APT were used in patients with eosinophilic esophagitis with controversial use.

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1e ALLERGY TESTS ON THE SKIN: THE REPEATED OPEN APPLICATION TEST (ROAT)

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The repeated open application test (ROAT) is a supplement to the conventional occluded patch test. It is a tool that can be used to support the determination of clinical relevance of patch test reactions. It requires a cooperative patient that gives consent to perform the ROAT. It is an open exposure use test that mimics the everyday use of topical products. Test substances, e.g. patients' own products or a patch test allergen are typically applied twice daily for seven days or more, to a well demarcated area on the forearm or upper arm close to the antecubital fossa. It is possible to test 2-3 products simultaneously on separate marked sites on the arms. The size of each test area is usually 5x5-cm^2 or 10x10-cm^2 and the amount of test substance applied may vary dependent on the substance/product in question. Both leave-on and rinse-off products may be tested. Positive reactions may appear after few or several days depending on the strength of allergic response and the dose applied.

KEY MESSAGES

- The ROAT is a controlled use test to support the clinical evaluation of the relevance of positive patch test reactions
- The ROAT requires a cooperative patient who gives consent to perform the test
- The test substance is usually applied twice daily for various number of days (7 or more)
- The application on a test site should be discontinued when a clearly visible eczematous reaction appears, and the patient should be instructed to contact the dermatologist

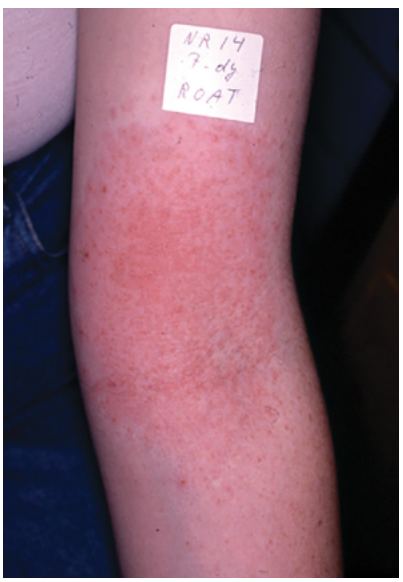

Figure 1 Positive (allergic) ROAT reaction (follicular reaction pattern with non-infiltrated erythema) to *Germall 115* after twice-daily applications for 1 week to the left upper-arm. *Germall 115*, also known as *Imidazolidinyl urea*, is an antimicrobial preservative used in cosmetics

A negative ROAT does not exclude that the patient is allergic to the substance, because the application period may have been too short or the test site not sensitive enough. Usually, the patient is instructed to stop application when a clearly visible eczematous reaction appears. Typically, a positive ROAT develops as follicular dermatitis (small papules) and erythema (Figures 1 and 2). Irritant ROAT reactions may occur depending on the individual ROAT design and type of test substance. Evaluation of responses may be strengthened by simultaneous testing with a control product on a neighboring test site. The ROAT is not only useful for determining the clinical relevance of allergic contact dermatitis to a particular allergen or product, it is

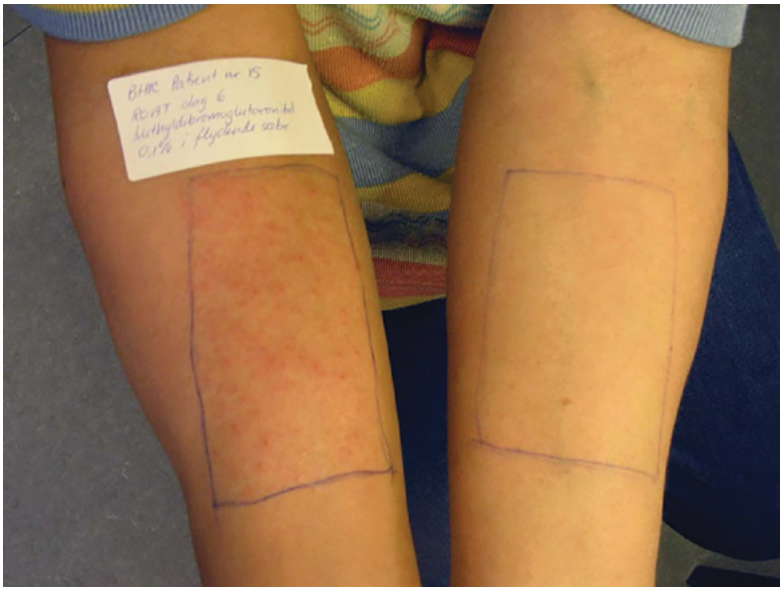

Figure 2 *Left field:* Positive (allergic) ROAT reaction (follicular reaction pattern) to liquid soap containing 0.1% Methydibromoglutaronitrile (MDBGN) following twice-daily application for 6 days; *Right field:* Negative reaction to the same liquid soap without MDBGN on Day 6. *MDBGN* is a preservative, frequently used in skin care products such as lotions, wet wipes, shampoo, and liquid soaps

also suitable for experimental comparative studies (e.g. application of scented product on the right arm and the same product but unscented on the left arm).

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1f ALLERGY TESTS ON THE SKIN: SKIN APPLICATION FOOD TEST (SAFT) AND FOOD CONTACT PROVOCATION TEST

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KEY MESSAGES

- There is a need for reliable methods for diagnosing immediate and delayed hypersensitivity reactions in children and adults without the need for a food challenge
- Double-blind, placebo-controlled food challenges continue to be the "gold standard for the diagnosis of food allergy"
- The relevance of a positive Skin Application Food Test (SAFT) should be carefully assessed, ruling out false positive reactions

RATIONAL FOR FOOD CONTACT PROVOCATION TEST

Food allergies are important in terms of the danger of anaphylaxis and also have a considerable impact on quality of life for many children. Food allergies affect between 6% and 8% of children, with some being especially important e.g. peanut allergy. In order to avoid inappropriate diets which often lead to distress, is important to make an appropriate etiologic diagnosis. Double-blind, placebo-controlled food challenges are the "gold standard for the diagnosis of food allergy". Skin prick testing (SPT) and *in vitro* measurements of specific–immunoglobulin (Ig)E (radioallergo-sorbent assay of CAP) have been used to diagnose e.g peanut allergy, but these tests indicate sensitization and not necessarily clinical allergy.

IgE-mediated Contact Urticaria (CoU) induced by foods and animal products, is one of the manifestations of allergy in childhood atopic dermatitis.

Some special food induced eruptions traditionally considered as non-allergic, resulted in a positive delayed SPK and Skin Application of Food, suggesting a delayed systemic hypersensitivity. This is the case of the Flagellate dermatitis developed after consumption of shiitake mushrooms.

There is a need for a reliable method for diagnosing immediate and delayed hypersensitivity reactions in children and adults without the need for a food challenge.

SKIN APPLICATION FOOD TEST (SAFT)

Atopy patch tests with occlusion times of >48 hours have been investigated in the diagnosis of allergy relating to intake foods. These studies commonly involve children with mixed or delayed hypersensitivity reactions as atopic dermatitis. The immediate skin application food test (I-SAFT) applying food to the skin prior to food challenge is sometimes used to identify children sensitive to very small quantities of allergen. If a wheal develops where the food is applied the challenge finishes and is considered positive. For peanut allergy positive I-SAFT was 82% specific and a combination of Skin Prick test of ≥ 8mm with a positive 1-SAFT and peanut specific IgE ≥0,37 kU/l were 88% specific with a sensitivity of 38%. Even combining these *in vitro* and *in vivo* techniques, food challenges should be considered the diagnostic gold standard. Contact sensitivity may not predict the outcome of oral food challenge.

Nevertheless in CoU the SAFT is useful as it is highly reproducible. Over more than 5 years, 175 patients with atopic dermatitis were investigated in a prospective follow-up study with SAFT. SAFT was more frequently positive in children 0-2 years than in older children. The SAFT repeated with-

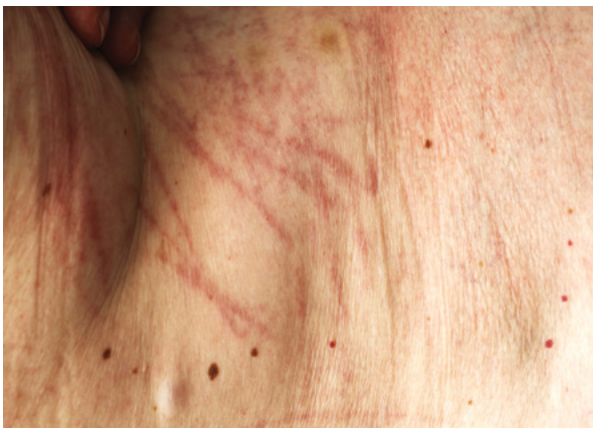

Figure 1 Flagellate Dermatitis of 48 hour evolution in trunk

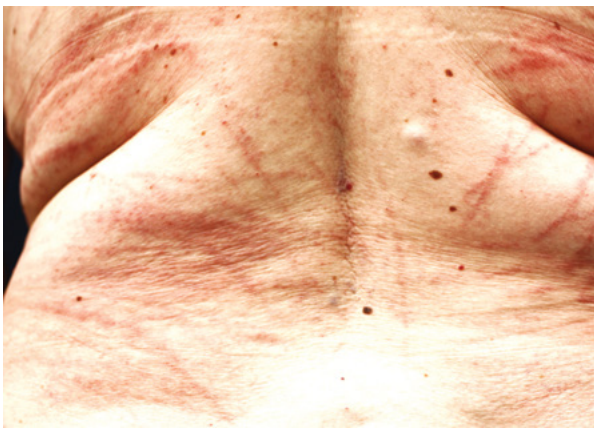

Figure 2 Flagellate Dermatitis induced by Shiitake mushroom

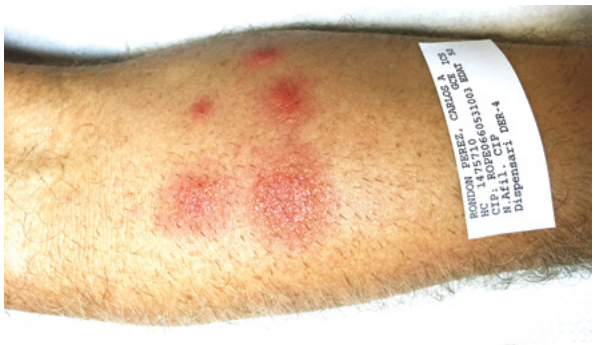

Figure 3 Positive delayed prick by prick test with Shiitake mushroom in a patient that previously developed a flagellate dermatitis

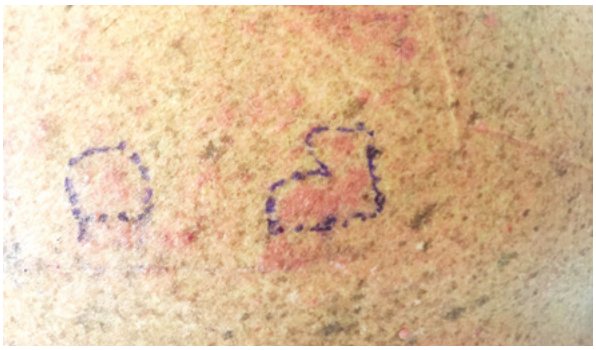

Figure 4 Positive delayed patch test (SAFT) with Shiitake mushroom, in a patient that previously developed a flagellate dermatitis

in a period of 1 year showed an agreement of at least 80%.

Flagellate dermatitis by shiitake mushrooms (lentinan) was first described by Nakamura, who reported 23 cases of shiitake dermatitis. The flagellate itchy erythema occurs with all forms of shiitake and appears 12-48 hours after intake mainly in the trunk (Figure 1, 2). The clinical suspicion and a positive oral-challenge test confirm the diagnosis. Positive delayed SPT and Shiitake patch test reproduce the eczematous character of this flagellate dermatosis (Figure 3, 4). However, positive tests in control subjects limit SPT and SAFT usefulness.

The relevance of a positive Skin Application Food Test (SAFT) should be carefully assessed ruling out false positive reactions, and requires standardization.

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1g ALLERGY TESTS ON THE SKIN: USE OF PHYSICAL PROVOCATION TESTS ON THE SKIN

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KEY MESSAGES

- Skin provocation testing should be performed to confirm diagnosis of inducible urticaria
- Wherever possible, provocation threshold testing should be performed before and during treatment
- Standardized skin provocation methods are available for most inducible urticaria forms

The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria recommends the use of provocation testing to diagnose chronic inducible urticaria (CIndU). Furthermore, the guidelines recommend using threshold measurements in skin provocation tests to allow for assessing disease activity and response to treatment. CIndU is a group of diseases that includes physical urticarias (symptomatic dermographism, cold and heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory angioedema) and CIndU with a non-physical trigger (cholinergic urticaria, contact urticaria and aquagenic urticaria). While the patient history is most important to suspect CIndU, provocation testing is necessary to confirm the diagnosis and to identify trigger thresholds that are useful for measuring and monitoring treatment responses.

GENERAL ASPECTS OF PHYSICAL PROVOCATION TESTS ON THE SKIN

The use of physical provocation tests on the skin should follow the current recommendations of the management of CIndU. If possible, antihistamines should be avoided for at least three days, and oral glucocorticoids for at least seven days before testing. If this is not possible because of the severity of the symptoms, provocation testing should, nevertheless, be performed but interpreted with caution. The skin area used for testing should be free of any skin disease and should not have been affected by urticaria in the last 24 hours. Documentation of the results of the provocation tests and the threshold testing should be performed on every occasion in the patient files, ideally following the recommendation for the documentation of CIndU provocation tests.

PROVOCATION TEST FOR SYMPTOMATIC DERMOGRAPHISM (SD, ALSO CALLED URTICARIA FACTITIA)

In SD, rubbing or scratching of the skin results in the development of itchy wheals within minutes. Stroking of the skin on the volar forearm or upper back with a smooth blunt object (for example a wooden spatula or a dermographometer) is used to diagnose SD. The provocation test is positive if an itchy wheal occurs at the site of provocation within ten minutes. A normal response is a short lasting (i.e. less than ten minutes) red line (red dermographism). A white dermographism can occur in atopic patients and is unrelated to SD. In some individuals, a non-itchy wheal develops which indicates simple dermographism, a common physiological variant. Both for diagnosis and threshold measurements, FricTest® can be used which is a plastic comb with four tips of different sizes. This induces a graded shearing force to the skin, allowing for determination of trigger thresholds, (Figure 1).

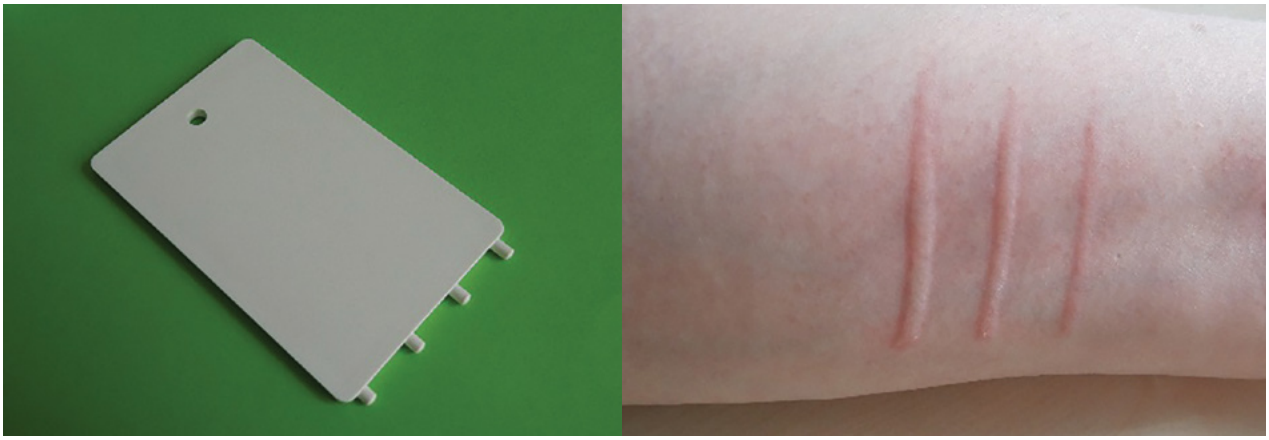

Figure 1 Skin provocation testing with FrictTest® (Moxie, Germany) in a patient with symptomatic dermographism

PROVOCATION AND THRESHOLD TESTING IN COLD AND HEAT URTICARIA

In cold urticaria (coldU), itchy wheals occur within minutes after contact with cold. Therefore, skin provocation tests are performed by applying cold, e.g. a melting ice cube enclosed in a plastic bag, to the skin. The diagnosis and threshold testing in cold urticaria is possible using TempTest®, which enables provoking the skin with a continuous temperature gradient from 4° to 44°C (Figure 2). TempTest® has the advantage of also providing information on heat urticaria, which is otherwise difficult to diagnose by provocation test. If a TempTest® is not available, a 44°C warm object or water bath should be used. Both, cold and heat urticaria provocation should be performed for five minutes and the skin should be inspected ten minutes after provocation testing.

PROVOCATION TESTING IN DELAYED PRESSURE URTICARIA (DPU)

In patients with DPU, swelling of the skin usually occurs 6 to 8 hours after application of pressure to the skin. For pressure provocation testing different methods have been described, e.g. suspension of weights over the shoulder (7kg on a 3cm shoulder strap for 15 minutes) or a dermographometer, which is applied perpendicular to the skin of the upper back for seventy seconds. Provocation testing is positive if a palpable swelling can be identified at the test site about 6 hours after provocation.

OTHER PHYSICAL SKIN PROVOCATION TESTS

Rare types of CIndU are solar urticaria, vibratory angioedema and aquagenic urticaria. If the history of the patient indicates one of these subforms of urticaria, specific provocation should be performed. For solar urticaria, photo testing is performed on the buttocks with UVA, UVB and, if indicated from the history, with visible light. The test is considered positive if a clearly visible wheal develops within ten minutes. In vibratory angioedema, itching and swelling are induced within minutes at the site of skin exposed to vibration. Here, provocation can be performed using a laboratory vortex. In aquagenic urticaria, a very rare form of CIndU, any source of water will result into a wheal response at the site of contact. To perform provocation tests on the skin, a towel soaked with body warm water is placed on the patients' trunk for up to 40 minutes. The test is positive if wheals, mostly 1 to 2 mm in size, develop within ten minutes after the end of provocation.

PROVOCATION TEST IN CHOLINERGIC URTICARIA (CHOLU)

CholU is a common non-physical CindU. To confirm CholU, patients should be subjected to moderate physical exercise, e.g. on a stationary bicycle. The exercise should lead to sweating of the patient and should then be carried out for up to 15 minutes, or until symptoms start occurring.

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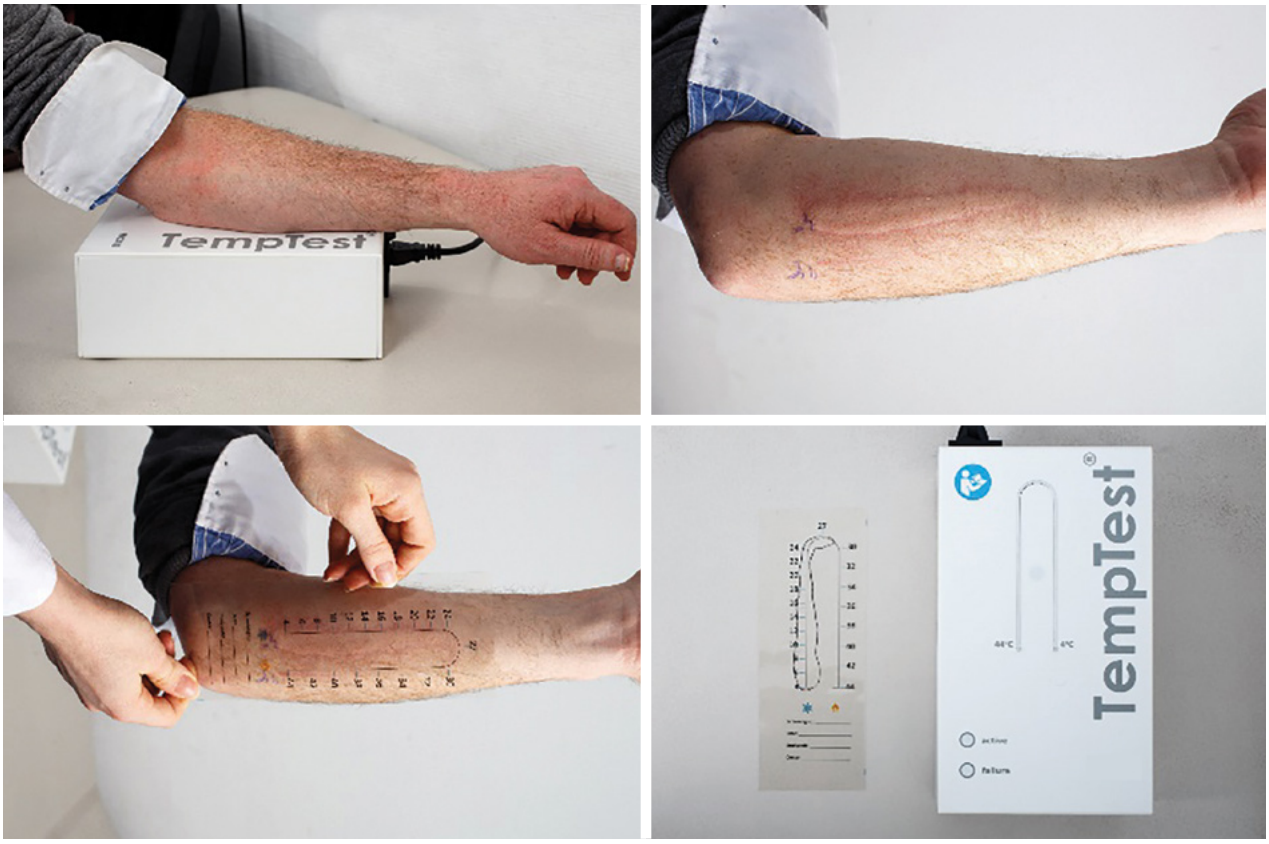

Figure 2 Skin provocation testing with TempTest® (Courage+Khazaka electronic, Germany) in a patient with cold urticaria. The forearm is placed on the device for 5 minutes and the highest temperature which induces a wheal (critical temperature threshold) is assessed after 10 minutes

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2 MOLECULAR DIAGNOSIS FOR SKIN ALLERGY

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KEY MESSAGES

- Skin testing is part of the diagnosis of allergic diseases, providing evidence of sensitization to food derived and inhalant allergens
- Allergen specific skin testing has been proven safe
- For routine diagnosis molecular testing is not expected within the near future due to regulatory issues

IgE mediated allergies are regarded as a modern epidemic, affecting the skin, respiratory and gastrointestinal tract and even the cardiovascular system.

ALLERGIC SENSITIZATION

During the sensitization phase allergens cross epithelial barriers and subsequently get into contact with the immune system. Allergens can be readily taken up by mucosal sites of the respiratory and the gastrointestinal tract and consequently, an IgE based immune response is mounted in atopic individuals. Recently, sensitization via the skin has been discussed to be relevant for certain foods such as peanut.

IN VITRO DIAGNOSIS - SKIN PRICK TESTING

Skin prick tests (SPTs) have been used since the 19th century by Charles Blackley and are still part of the state of the art diagnosis for allergies.

EXTRACT BASED VERSUS MOLECULAR TESTING

To date, extracts prepared from the allergen sources are used and approved for SPT (Figure 1). However, these extracts are not well standardized regarding the individual allergen content and may vary from batch to batch considerably. Since this applies to the majority of food extracts, prick to prick testing is preferred, using the potential allergen source directly.

During the last 3 decades advanced molecular biology methods allowed production of individual allergens, either recombinant or natural. This allergen specific approach for diagnostic purposes is known as molecular diagnosis or component resolved diagnosis (CRD). So far, only proof of concept studies on the application of purified recombinant allergens were performed such as recombinant Mal d 1 and Mal d 4 from apple. Recent studies also used recombinant Mal d 1 and Bet v 1 produced under GMP conditions, a requirement for *in vivo* test application.

Another study used purified natural peanut allergens, Ara h 1, Ara h 2, Ara h 3, and Ara h 6 for SPTs in both adult and pediatric cohorts of allergic patients. The application of these purified food allergens was safe, provided positive results and the reaction was dose dependent. However, skin reactions to an individual allergen could not be related to the severity of symptoms.

Currently, a natural peach extract enriched in Pru p 3 and a date extract containing date profilin are approved for diagnostic testing in some European countries.

CONCLUSIONS AND OUTLOOK

SPTs are well established for routine diagnosis, comparatively cheap, easy to perform, enabling a number of simultaneous tests and the readout is available after 20 minutes. Yet, in parallel to IgE based *in vitro* diagnosis the re-

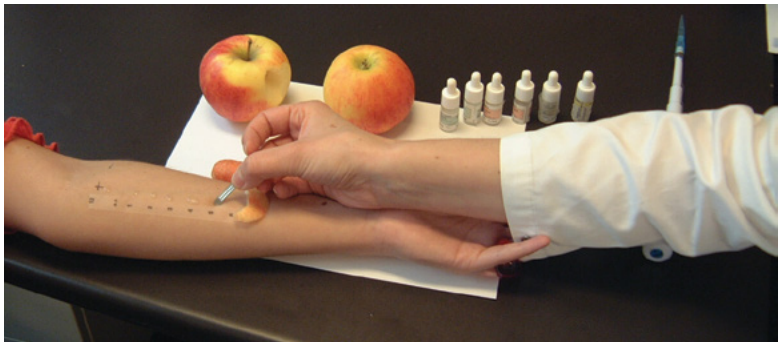

Figure 1 Skin Prick test with test solution and fresh apple and carrot

sults provide evidence of allergic sensitization and do not always correlate with symptoms to the allergen source. Although CRD is available for SPTs official approval is needed for each single allergen. Therefore, introduction of CRD for routine application is not expected in the near future.

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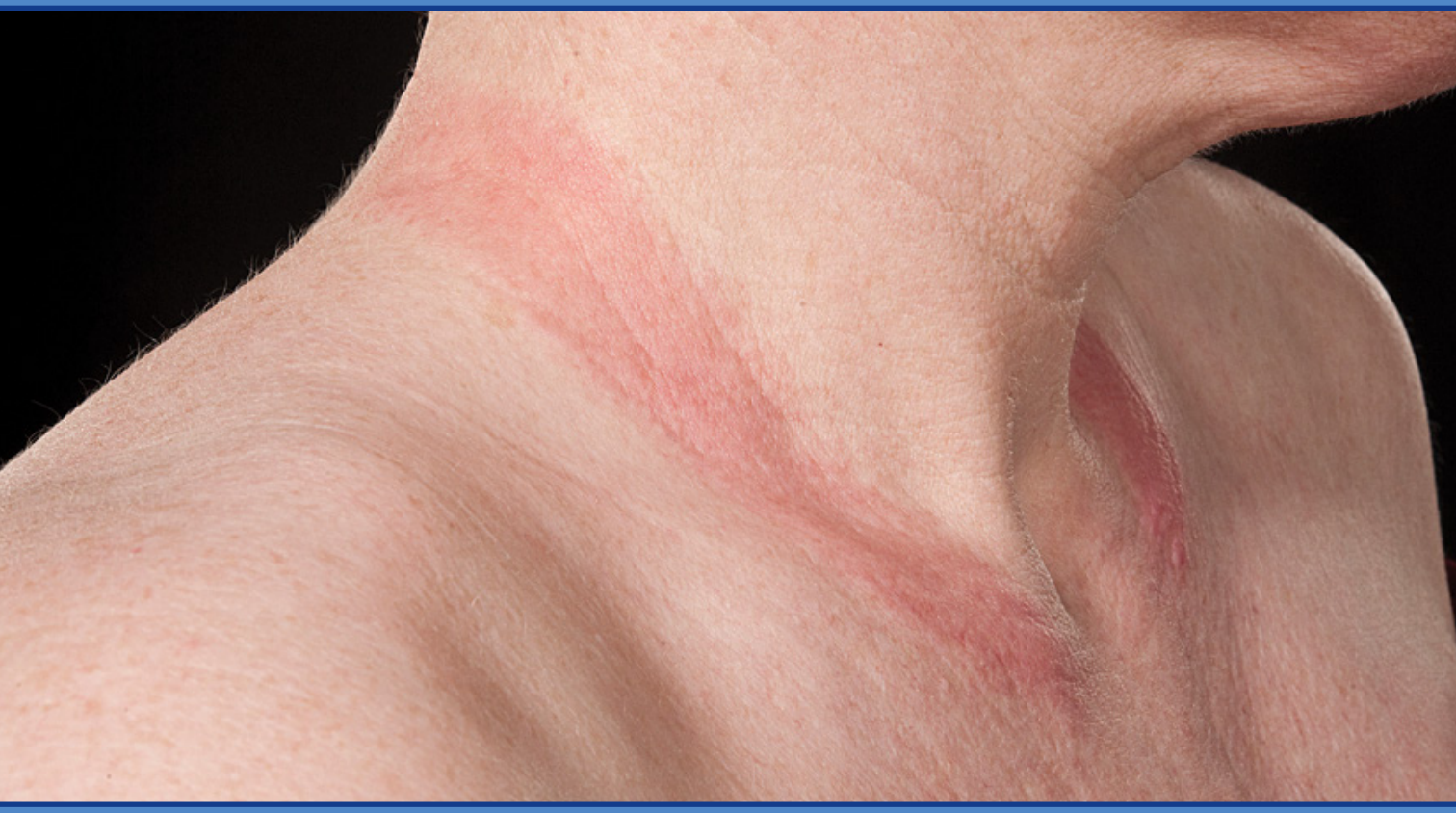
Section E



ALLERGIC SKIN DISEASES

* Bradykinin-induced angioedema
* Atopic dermatitis
* Contact dermatitis
* Photocontact dermatitis and photoallergic reactions
* Cutaneous drug hypersensitivity reactions
* Mastocytosis
* Urticaria and angioedema
* Skin manifestations in food allergy
* Food-dependent exercise-induced urticaria and anaphylaxis
* Epidermal skin barrier and food allergy

1a BRADYKININ-INDUCED ANGIOEDEMA: DRUG-INDUCED ANGIOEDEMA

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KEY MESSAGES

- Drugs interfering with the renin–angiotensin system, respectively the kinin system may cause bradykinin mediated angioedema
- There are no standard laboratory or skin tests to diagnose these pharmacological side effects
- Drug induced bradykinin mediated angioedema frequently affects the head and neck region, thus being life-threatening
- ACE-inhibitors are the most frequent cause of drug induced bradykinin mediated angioedema, either alone or in combination with other drugs interfering with the renin–angiotensin or the kinin system
- There are currently no licensed drugs to treat these angioedema attacks effectively

Numerous drugs can cause angioedema, either by IgE-mediated immediate type allergy or by non-allergic ("pseudoallergic") mechanisms. In immediate-type allergy to drugs, e.g. betalactams, an isolated angioedema without other manifestations is uncommon. NSAIDs are probably the most common elicitors of drug-induced angioedema. Usually, this side effect is mediated by histamine and the symptoms are responsive to anti-allergic drugs.

However, some drugs can cause bradykinin-mediated angioedema, either by increased bradykinin formation or by inhibited bradykinin degradation. Bradykinin is a potent vasodilator and it increases vascular permeability. Bradykinin is formed by the kinin system, consisting of (pre)-kallikrein and factor XII. Upon activation of the kinin system, a precursor kininogen is cleaved by kallikrein to release bradykinin. Once generated, bradykinin is quickly degraded by angiotensin-converting enzyme (ACE) and neutral endopeptidase, respectively. Other important degrading enzymes are aminopeptidase P, carboxypeptidase N and dipeptidyl peptidase IV. Most often, this balance between formation and degradation is disturbed by ACE-inhibitors.

ACE is critical in the degradation of bradykinin, which is hypothesised to accumulate excessively in 0.12-0.6% of patients taking ACE inhibitors, the risk in african american persons is many times higher. ACE-inhibitor-induced angioedema frequently affects the head and neck region, including the tongue, larynx and pharynx, thus being life-threatening (Figure 1). Presenting symptoms include shortness of breath, dysphagia, stridor, and hoarseness.

Patients can present with symptoms any time from one day to years after starting an ACE inhibitor. There is no standard laboratory test or skin test to diagnose ACE-inhibitor-induced angioedema, the diagnosis is based on the above mentioned symptoms when occurring under therapy with ACE-inhibitors. As the symptoms are bradykinin-mediated, the bradykinin-receptor-2-antagonist icatibant was considered to be effective, however recent randomised controlled trials exhibit contradictory results with the use of icatibant.

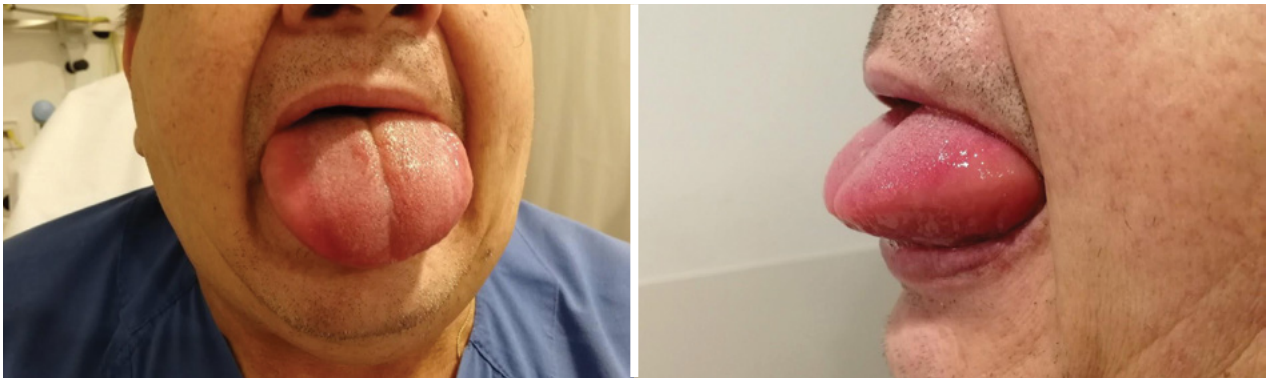

Figure 1 ACE-inhibitor induced angioedema at typical location. Symptoms were quickly regressive after off-label-use of icatibant

Gliptins or dipeptidylpeptidase-4 inhibitors are blood glucose-lowering agents from the group of antidiabetics used for the treatment of type 2 diabetes. Their effects are based on the inhibition of the enzyme dipeptidylpeptidase-IV (DPP-IV), which is responsible for the degradation of the body's own incretin (metabolic hormones that stimulate a decrease in blood glucose levels). DPP-IV is also one of the enzymes degrading bradykinin. It was found that gliptins alone did not increase the incidence of angioedema significantly unless patients concomitantly received ACE inhibitors.

Neprilysin, also known as neutral endopeptidase, is a metalloprotease that breaks down multiple different peptides, including bradykinin. Inhibitors of neprilysin are used for treatment of systolic heart failure. Its concomitant use with ACE inhibitors is contraindicated, due to a high risk of angioedema. It's administered in combination with valsartan, exhibiting a risk of angioedema similar to that observed with ACE inhibitors.

The pathophysiology of angioedema induced by Angiotensin II type 1 receptor blockers (ARB) is still unknown, but there is some evidence for the involvement of the bradykinin 2 receptor. There are some reported cases of ARB induced angioedema, but the overall risk seems to be rather low.

The renin inhibitor aliskiren, an antihypertensive agent, may cause angioedema which is thought to be bradykinin-mediated. A meta-analysis found a 0.4% incidence of angioedema in subjects treated with aliskiren.

Tissue plasminogen activator (tPA) is used for thrombolysis in myocardial infarction, stroke, and pulmonary embolisms. tPA catalyzes the conversion of plasminogen to plasmin, the latter activates the kinin system via factor XII. In 2.7% of the patients tPA leads to angioedema, patients pretreated with ACE inhibitors have a much higher risk

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1b BRADYKININ-INDUCED ANGIOEDEMA: HEREDITARY ANGIOEDEMA

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OVERVIEW

Hereditary angioedema (HAE) is a disease characterized by recurrent episodes of angioedema without urticaria localized at subcutaneous and submucosal sites transmitted as autosomal dominant trait (Figure 1). The large majority of patients experience both angioedema of the skin and of the gastrointestinal mucosa. Laryngeal oedema occurs in 50% of patients and accounts for around 5% of all angioedema episodes. In absence of diagnosis, laryngeal oedema can be cause of death in nearly 50% of C1-INH-HAE patients.

KEY MESSAGES

- Hereditary angioedema (HAE) is a rare genetic disease characterized by recurrent episodes of unpredictable, self-limiting angioedema without urticaria localized at subcutaneous and submucosal sites
- Airway involvement can be life-threatening when affecting the larynx, while edema of the gastrointestinal mucosa can mimic an acute surgical condition, leading to iatrogenic invasive medical procedures
- Best characterized is the HAE phenotype with functional complement C1 inhibitor (C1-INH) deficiency. In the absence of their principle controller, activation of the contact and the kallikrein/kinin systems leads to vasoactive bradykinin liberation: recognized to orchestrate vascular permeability and provoke angioedema manifestations
- In the last decades specific bradykinin-targeted drugs have been developed and approved for the treatment of acute angioedema attacks (on demand therapy, ODT), short-term and long-term prevention of recurrent angioedema episodes (STP and LTP, respectively)

EPIDEMIOLOGY AND PATHOGENESIS

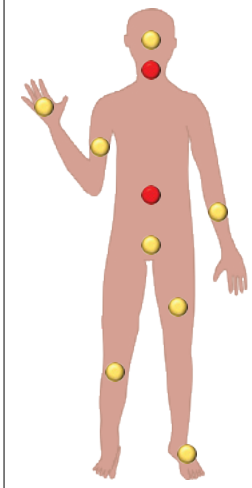
Angioedema results from transient increase in vascular permeability with local fluid extravasation. Prevalence is similar worldwide and not below 1:60,000.

Most common form of HAE is genetic deficiency of C1-inhibitor (C1-INH-HAE) due to heterozygous mutations in C1-INH gene (*SERPING1*) that cause antigenic, and/or functional plasma C1-INH levels below 50% of normal (types I and II, respectively). Four separate forms of HAE with normal C1-INH (nl-C1-INH-HAE) also exist: three depend on genetic variants in factor XII, angiopoietin-1 and plasminogen genes (FXII-HAE, Plg-HAE, Angpt1-HAE). In the last form angioedema symptoms segregate in the families, but the genetic defect is yet unknown (U-HAE) (Figure 2) .

HAE prototype is the form with C1-INH deficiency: it is bradykinin-mediated and cured by bradykinin targeted drugs. C1-INH controls the activity of the two enzymes, factor XIIa and plasma kallikrein, that lead to bradykinin release (Figure 3). The link between C1-INH deficiency and angioedema is obvious. The pathophysiology of nlC1-INH- HAE is likely to be also bradykinin mediated, but final experimental proof is still waiting.

DIAGNOSIS

Diagnosis of HAE is maintained through complement measurements in plasma (C1-INH protein



Clinical presentation of HAE due to C1-INH deficiency

- Symptoms are recurrent, noninflammatory, nonpitting, non-pruritic, self-limiting edema of:
  - Subcutaneous sites (peripheral, facial, genital edema)
  - Subcmucosal sites (gastrointestinal, oro-pharyngeal, laryngeal edema)
- Duration of each angioedema attack ranges between 1 and 3 days
  - Could be more than 3 days when multiple locations are involved
- Frequency of recurrences varies among patients and within the same patient over time:
  - From life-long asymptomatic to 3 attacks/week
- Mortality due to HAE is >25% in undiagnosed patients

Figure 1 Clinical presentation of HAE due to C1-INH deficiency. Cutaneous symptoms last 24-72 hours and more often affect limbs then face, trunk and genitals. Angioedema of the gastrointestinal mucosa causes temporary bowel occlusion with attending pain, vomiting, diarrhoea up to collapse for dehydration. They resolve within maximum 48 hours, but misdiagnosis can lead to unnecessary surgery. Involvement of the upper airways is life-threatening and can cause death by asphyxiation in up to 50% of undiagnosed patients. C1-INH – C1 esterase inhibitor; HAE – hereditary angioedema

and function; C4 protein) and genotyping for mutations in *F12*, *PLG* and *ANGPT1*. Diagnosis of U-HAE relays on the presence of family inheritance.

TREATMENT

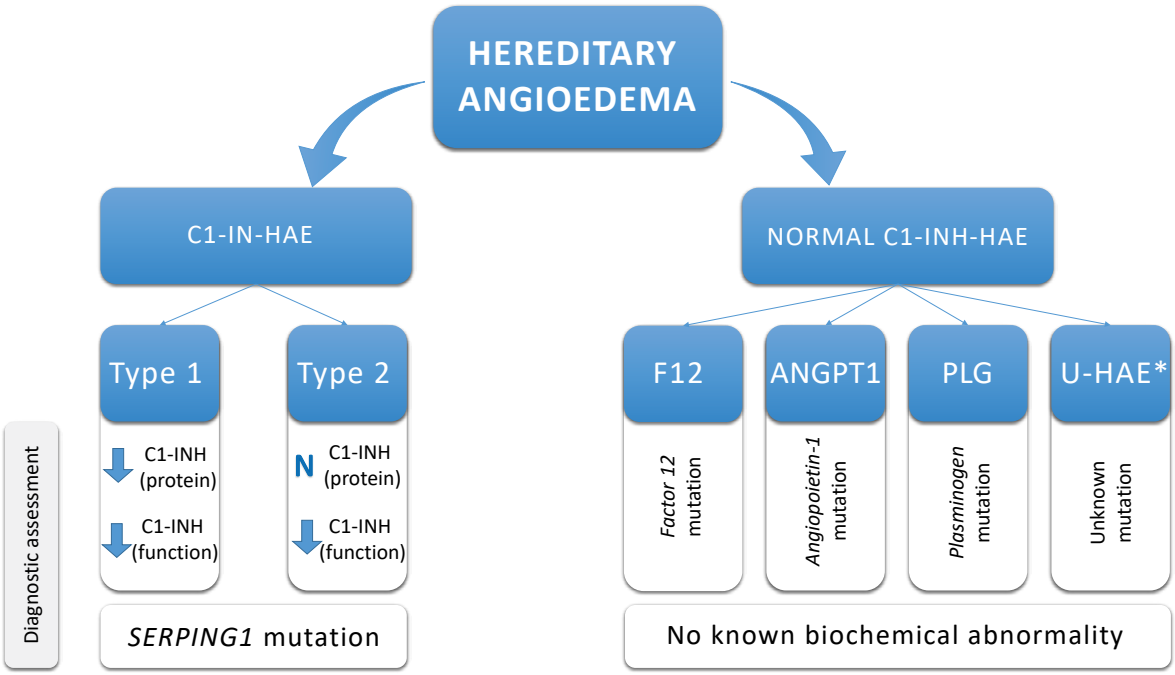
Treatment strategies in C1-INH-HAE distinguish management of acute angioedema manifestations (on demand treatment, ODT), short-term prophylaxis (STP), and long-term prophylaxis (LTP) (Table 1). STP aims at preventing angioedema in specific settings at risk for inducing life-threatening attacks, such as deemed invasive medical procedures. ODT and LTP are complementary: ODT avoids life-threatening consequences and shortens attack duration and severity reducing disease related morbidity and disability. LTP is added to ODT when disease control is not satisfactory. Attenuated androgens (danazol up to 200 mg/day), since 1976, and plasma derived C1-INH (twice weekly i.v. infusions), since 2009, are established LTP approaches. In

TABLE 1

Treatment of HAE		
ODT	pdC1-INH / iv	20 U/kg / iv
	rhC1-INH / iv	50 U/kg / iv
	icatibant / sc	30 mg (10 mg/mL) / single dose vial / sc
	ecallantide / sc	30 mg (10 mg/mL) in 3 separate injections / sc
STP	C1-INH / iv	20 U/kg / iv no more than 6 hours before procedure
	Androgens / po	200-600 mg 3 days before and 2 days after procedure
LTP	Androgens / po	Lowest clinically effective dose (up to 200 mg/day) with danazol
	C1-INH / iv	1000 U/every 3-4 days scale up or down based on clinical response
	C1-INH / sc	60 U/kg / twice weekly
	lanadelumab / sc	300 mg/ (100 mg/mL) every 2 weeks, consider every 4 weeks after 6 months

On demand therapy (ODT) is prescribed when C1-INH-HAE is first diagnosed. ODT can be performed replacing C1-INH with plasma derived (pdC1-INH, Berinert and Cinryze), and recombinant (rhC1-INH, Ruconest) products given intravenously / iv/, or with the bradykinin antagonist icatibant (Firazyr), or the kallikrein inhibitor ecallantide (Kalbitor, US only) given subcutaneously /sc/. These treatments reduce severity and duration of attacks allowing disease control. Long-term prophylaxis (LTP) is given in addition if disease control (frequency and severity of angioedema attacks) is not satisfactory. Danazol, stanozolol and oxandrolone have been widely used since 1980's in C1-INH-HAE showing a reasonable risk efficacy balance in patients with severe disease. Today subcutaneously administered plasma derived C1-INH and the anti-plasma-kallikrein monoclonal antibody lanadelumab are approved for LTP. Short-term prophylaxis (STP) aims at preventing angioedema in specific settings, for example invasive medical procedures. Nevertheless, STP can also be used to avoid attacks in situation where it could create personal or social discomfort.

A



B

TEST	HEREDITARY ANGIOEDEMA					
	C1-INH-HAE Type 1	C1-INH-HAE Type 2	FXII-HAE	ANGPT1-HAE	PLG-HAE	U-HAE
Genotyping	*SERPING1 variants*	*SERPING1 variants*	*Factor 12 variants*	*Angiopoietin-1 variant*	*Plasminogen variants*	Unknown*
Plasma C1-INH (protein)	Less than 50%	N or higher	N	N	N	N
Plasma C1-INH (activity)	Less than 50%	Less than 50%	N	N	N	N
Plasma C4 (protein)	Less than 50%	Less than 50%	N	N	N	N

Figure 2 Hereditary angioedema: phenotypes and diagnostic assessment. A. Phenotypes / genotypes of HAE. * Diagnosis established by exclusion. C1-INH - C1 esterase inhibitor; C1-INH-HAE – hereditary angioedema due to C1 inhibitor deficiency; F12 – coagulation Factor 12; ANGPT1 – angioepoietin-1; PLG – plasminogen; U-HAE– hereditary angioedema due to unknown (U) mutation. B. Diagnostic assessment of HAE. C1-INH – C1 esterase inhibitor; C1-INH-HAE – hereditary angioedema due to C1 inhibitor deficiency; F12-HAE – hereditary angioedema due to mutation in the coagulation Factor 12 gene; ANGPT1-HAE – hereditary angioedema due to mutation in the Angiopoieting-1 gene; U-HAE – hereditary angioedema due to unknown mutation; C4 – complement C4; N – normal. * Diagnosis established by exclusion

addition, subcutaneously administered plasma derived C1-INH and the anti-plasma-kallikrein monoclonal antibody lanadelumab were recently approved for LTP. Availability of different drugs will facilitate individualized approaches coping optimal safety/efficacy profiles to disease variability. Novel therapies potentially effective for both ODT and LTP are in advanced clinical development envisaging additional tools for optimizing therapeutic approaches.

Treatment options for nlC1-INH-HAE are instead non-existing. Assuming bradykinin mediated symptoms, off label approaches with bradykinin targeted drugs have been attempted, but evidence for efficacy remains highly elusive.

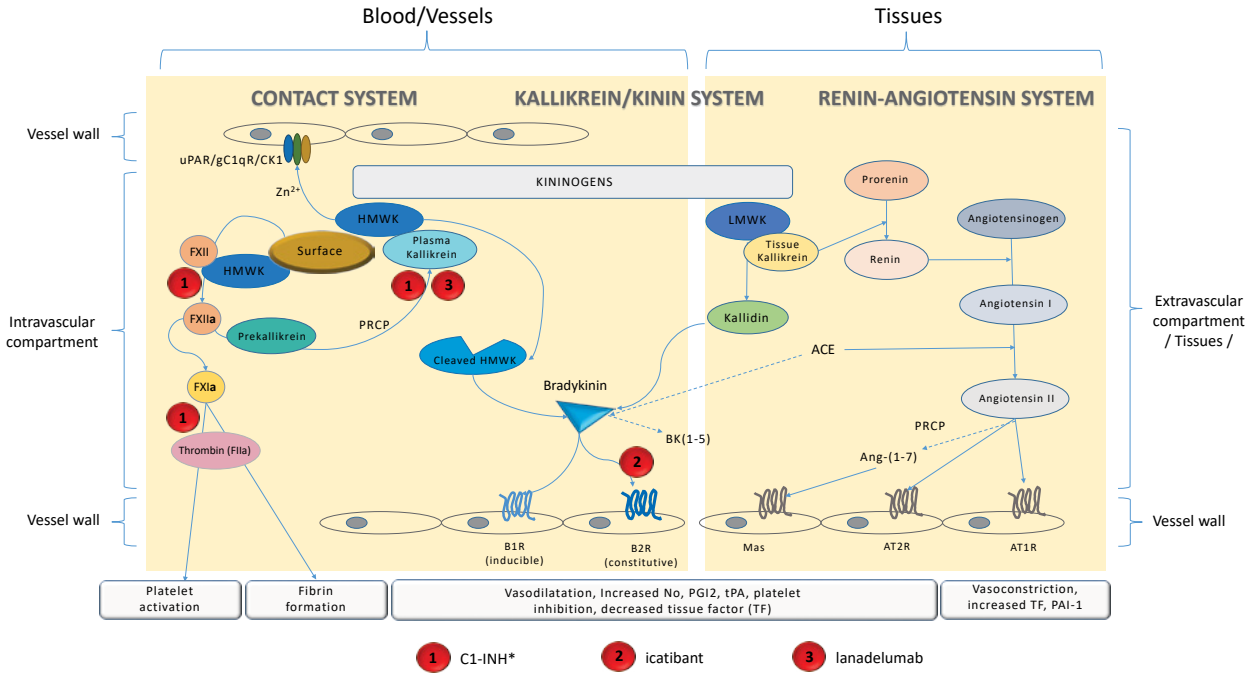


Figure 3 Interaction of the contact activation system (CAS), the kallikrein/kinin system (KKS), and the renin-angiotensin system (RAS) in the intravascular compartment, vessel wall and extravascular tissue. The Contact activation system (CAS) is described as a surface-activated defense system which comprises of three major proteins: factor XII (FXII), prekallikrein, and plasma kallikrein. Its activation in vivo is associated with various processes and disease states, while there is no described physiologic process mediated by the contact system. The CAS depends upon activation of the zymogen FXII into an active enzyme FXIIa. Classically this is described upon contact with a negatively charged surface, although it arises also on neutral and positively charged surfaces at a slower rate. Activated FXIIa then activates prekallikrein to form plasma kallikrein. This process is accelerated by the presence of high-molecular-weight kininogen (HMWK). Another way to activate prekallikrein to active plasma kallikrein is in a FXII-independent manner: through another serine protease, prolycarboxypeptidase (PRCP). The kallikrein/kinin system (KKS) consists of plasma kallikrein cleaving HMWK to liberate vasoactive bradykinin (BK). It binds to its constitutively expressed bradykinin 2 receptor (B2R), or to the inducible in inflammatory states bradykinin 1 receptor (B1R). Activation of these receptors further modulates the endothelial cells and impairs vascular permeability. HMWK and FXII bind in a Zn^{2+}-dependent manner to the multiprotein receptor system (urokinase plasminogen activator receptor /uPAR/, gC1qR, and cytokeratin 1 /CK1/). FXII stimulates cell proliferation and angiogenesis through uPAR and HMWK blocks both. The tissue-derived low-molecular weight kininogen (LMWK) is cleaved by tissue kallikrein to kallidin ready to liberate bradykinin. Tissue kallikrein interacts with the renin-angiotensin system (RAS) which on the other hand has an effector function on the vascular tone, thrombosis risk, blood pressure and fluid balance. * C1-INH controls other processes not shown in the figure. It has inhibitory protease activity on the Contact system (FXII, kallikrein – listed above), the Complement system (C1s, C1r, MASP2), the Coagulation system (FXI, thrombin), the Fibrinolytic system (plasmin, tissue plasminogen activator). C1-INH has also non-inhibitory interactions with endogenous proteins (C3b, fibrin, laminin), glycosaminoglycans (heparin, heparan sulfate), cells (neutrophils, macrophages, endothelial cells), infectious agents (bacteria, parasites, endotoxins)

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2a ATOPIC DERMATITIS: EPIDEMIOLOGY OF ATOPIC DERMATITIS

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ATOPIC DERMATITIS CONTEXT

Atopic Dermatitis (AD, syn. atopic eczema) affects around 20% of children and 5-8% of adults in developed countries and is associated with a significant socio-economic and psychological burden, in particular an increase in anxiety and depression as well as attention-deficit hyperactivity disorder.

The Global Burden of Disease (GBD) Study 2017 shows AD as the skin condition with the highest disability-adjusted life year (DALY) score (128.7 per 100,000 people) amongst all skin diseases, placing it as the 21st cause of non-fatal burden among all diseases. The prevalence is highest in children and rises again from middle age (Figure 1).

Loss-of-function (Lof) mutations in the filaggrin (*FLG*) gene are the main genetic risk factor for AD, resulting in 3-4 times higher odds of developing the disease, compared to those without a *FLG* LoF mutation. This genetic predisposition, in combination with environmental risk factors, such as childhood upbringing in urban areas, reduced UV exposure, environmental pollutants, cigarette smoking, and water hardness are thought to lead to the development of AD.

KEY MESSAGES

- AD poses the highest global non-fatal burden of all skin diseases, ranking 21st among all diseases
- AD prevalence tend to be highest in affluent country settings, most likely driven by lifestyle and environmental factors
- While the epidemiology of AD in children is well researched, more studies are required to examine the burden, co-morbidities and risk factors of adult (onset) AD

There is also a close association between AD and food and respiratory allergies.

In adults, an increased risk of cardiovascular disease, certain cancers, such as lymphoma, as well as a range of autoimmune diseases has also been described.

GLOBAL VARIATION

AD is a global phenomenon, with prevalence ranging from around 1.5% to 7.4% across age groups. There are marked differences in the prevalence between countries for both adults and children, with the highest burden observed in high income countries, such as USA, Canada, UK, France, Norway, Finland, Japan and Sweden (Figure 2).

TIME TRENDS

According to the International Study of Asthma and Allergies in Childhood, whilst the incidence of AD has increased by 2-3 fold in the past decades in industrialised countries, it has reached a plateau in the countries with highest prevalence such as the UK and Sweden. Prevalence continues to rise in low-income countries such as South East Asia. Such trend data is currently not available for adults.

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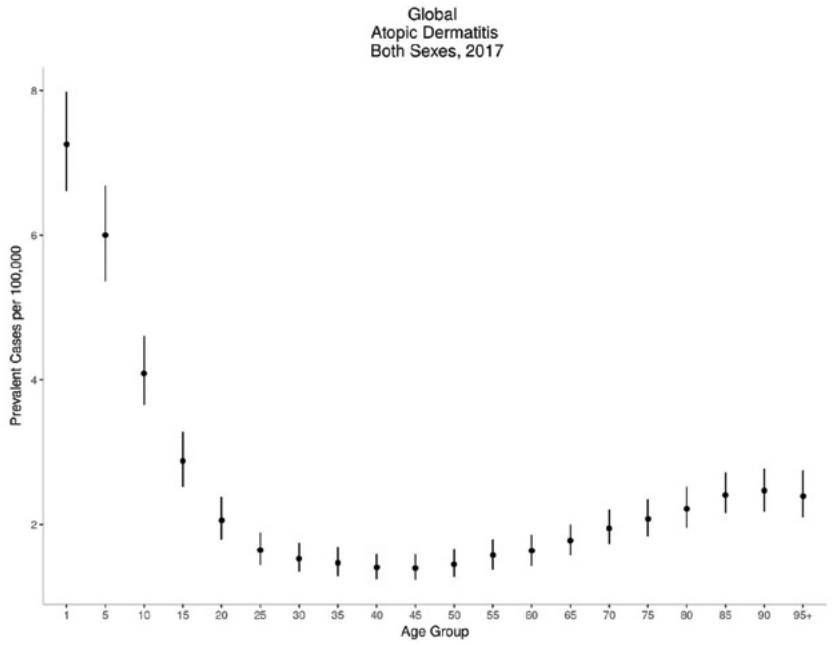

Figure 1 Global prevalent cases of atopic dermatitis per 100,000 for age group (in years). The burden of atopic dermatitis is highest in childhood and adolescents, with a gradual increase seen from middle age [source: Global Burden of Disease project 2017 data, Institute for Health Metrics and Evaluation, University of Washington, Seattle, US]

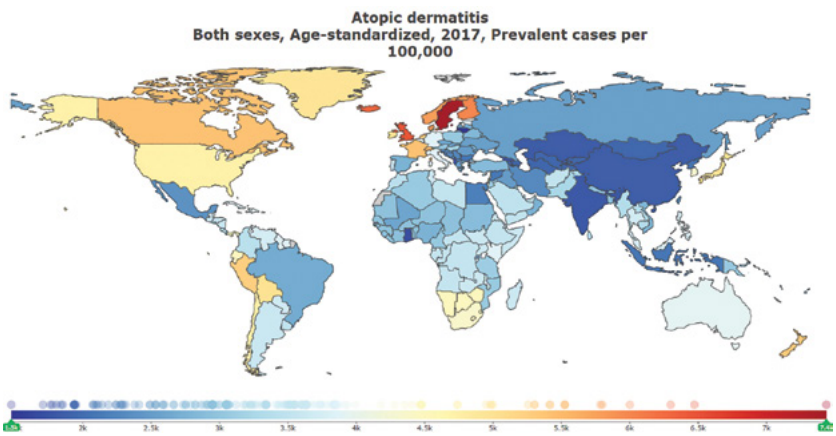

Figure 2 Global age-standardised atopic dermatitis burden (both sexes combined), prevalent cases per 100,000, ranging from blue (low prevalence areas) to red (high prevalence areas) [source: Global Burden of Disease project 2017 data, Institute for Health Metrics and Evaluation, University of Washington, Seattle, US]

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2b ATOPIC DERMATITIS: IMMUNOLOGICAL MECHANISM OF ATOPIC DERMATITIS

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KEY MESSAGES

- Initiation of atopic dermatitis involves both the innate immune response and the adaptive immune response
- In atopic skin, CD4+ T cells predominate in the cellular infiltrate
- The immune response in atopic dermatitis is skewed towards Th2

Atopic dermatitis (AD) is a complex disease involving impaired barrier function, abnormalities of the immune mechanism, and environmental risk factors. Which of the two major pathophysiological abnormalities—the epidermal dysfunction or the cutaneous inflammation—drives the primary disease is still being debated, but they clearly interact (Figure 1).

T cell infiltration predominates in the lesional AD skin, mainly with activated CD4+ T cells but also with increased numbers of dendritic cells, activated eosinophils and mast cells. Innate immune mechanisms, such as keratinocytes and type-2 innate lymphoid cells together with epithelial-derived cytokines such as thymal stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33, are involved in initiating the immune activation in a T-helper (Th)2 direction. In agreement with this, AD in the acute lesions has traditionally been perceived to be a Th2-mediated disease with overexpression of Th2 cytokines such as IL-4, IL-5, and IL-13 (Figure 2). In chronic AD lesions, Th1 cells are also present. Th2 cytokines, especially IL-4 and IL-13, have been shown to induce TSLP production by keratinocytes and to decrease the production of antimicrobial peptides and filaggrin, leading to further inflammation and barrier dysfunction. Also, in active AD disease there is a correlation between severity and a reduced diversity of skin microbiota, and increased colonization by *Staphylococcus aureus* may be because of the Th2-dominated inflammation.

The idea that AD is a Th2-mediated disease has been challenged in recent years, since Th17 cells (producing IL-17) and Th22 cells (producing IL-22 and tumour necrosis factor alpha) have been found in both acute and chronic lesional AD skin. The data suggest that there may be different endotypes depending on whether it is acute or chronic disease, on whether it

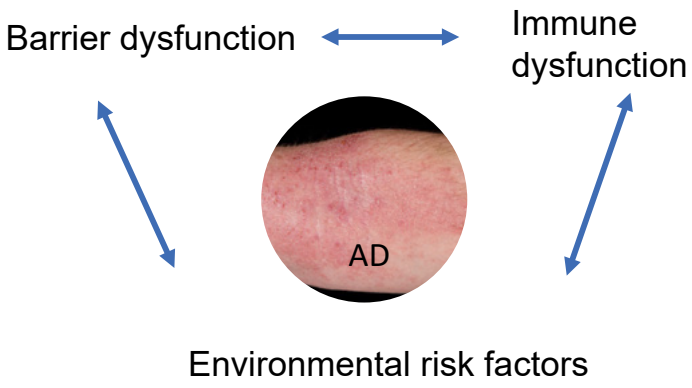

Figure 1 Important factors for atopic dermatitis

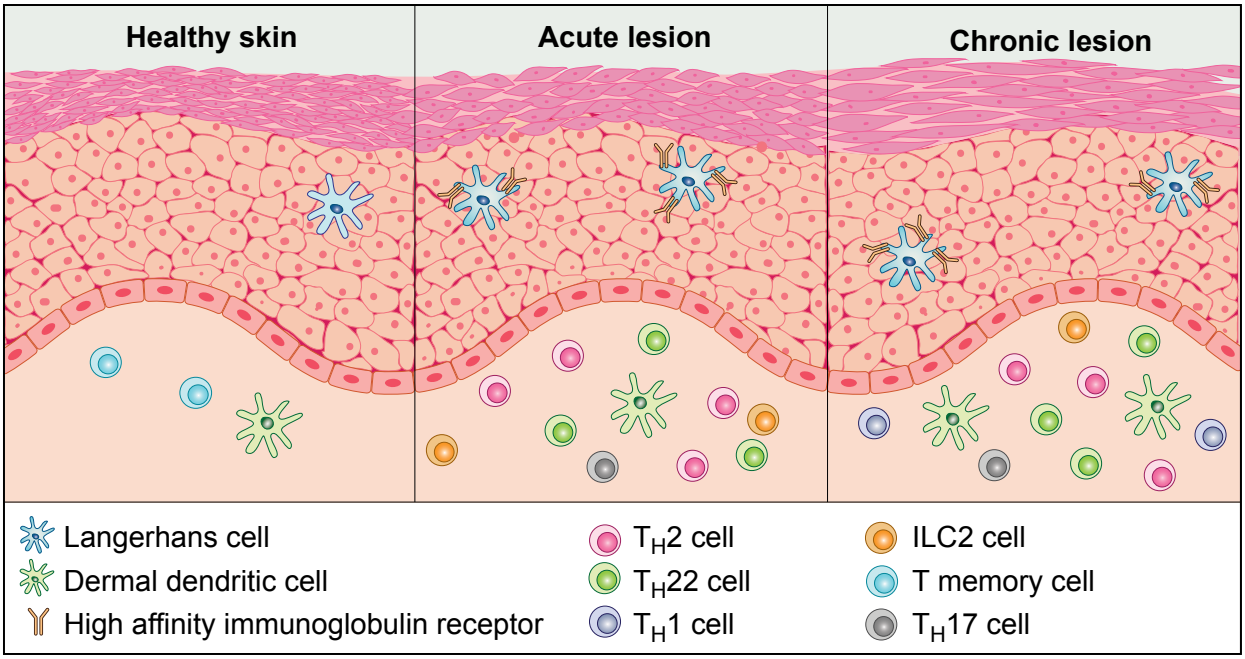

Figure 2 Schematic drawing of the immune cells in healthy skin compared to acute or chronic atopic skin

is paediatric or adult disease, and on different ethnicities, where in Asians with AD Th22 and Th17 cells appear to play an important role.

Eighty percent of patients with AD have high IgE levels, and AD patients can be grouped into the extrinsic (high IgE) and intrinsic (normal IgE) types. In contrast to allergic rhinitis, the role of high IgE in the majority of patients with AD is poorly understood, and it may be an epi-phenomenon.

Several other cells and chemokines/cytokines are involved in AD, including the T cell cytokine IL-31. IL-31 signals directly to neurons and induces pruritus, and the levels in serum correlate with disease severity. However, blocking of IL-31 only appears to reduce pruritis and not the severity of disease.

New knowledge of the important mediators in AD has led to new targets for treatment. One drug that blocks IL-4 and IL-13 is already registered, and several new treatments are underway, which will hopefully give us better treatment options and a better understanding of the disease mechanism.

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2c ATOPIC DERMATITIS: SKIN BARRIER PATHOBIOLOGY IN ATOPIC DERMATITIS

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KEY MESSAGES

- Impaired skin barrier is fundamental in the pathogenesis of atopic dermatitis
- Skin barrier alterations can be genetically determined and/or acquired, and often occur together in one patient
- Improvement of skin barrier is essential in the management of AD, and can also help in the prevention of this disease

Compared to other epithelial surfaces, the skin barrier has two major structures, the stratum corneum and the tight junction layer in the stratum granulosum of the epidermis. This combined barrier consists of cells (keratinocytes, corneocytes), intracellular structural proteins (filaggrin, involucrin, loricrin, keratins etc.), extracellular lipid lamellae with extracellular proteins (intercellular lipids, proteases, protease inhibitors) and adhesion structures (tight junctions, corneodesmosomes). Simplistically the brick-mortar hypothesis may describe its construction, as the bricks are represented by the cells, and the intercellular material is considered as mortar.

AD is a multifactorial immune-mediated inflammation of the skin that is driven by interactions of genetic and environmental factors. Besides over-reactive adaptive and dysregulated innate immune responses, the most important alterations that lead to the initiation and maintenance of the disease are impaired skin barrier functions (Figure 1). Impaired epidermal barrier not only allows the increased transepidermal water loss and penetration of environmental antigens but as an adjuvant can induce Th2 type inflammation in the skin. The persistent Th2 type inflammation in turn can cause further attenuation of the skin barrier, leading to a vicious circle and confirming the outside-to-inside hypothesis of allergic diseases, among others atopic dermatitis (AD).

One basic component of this barrier is filaggrin (FLG), which may show both genetic and acquired alterations. In the recent years it has been described, that about 20-60% of AD patients carry two loss-of-function mutations of the profilaggrin gene (R501X and 2282del4). Other genetic alterations, which can result in

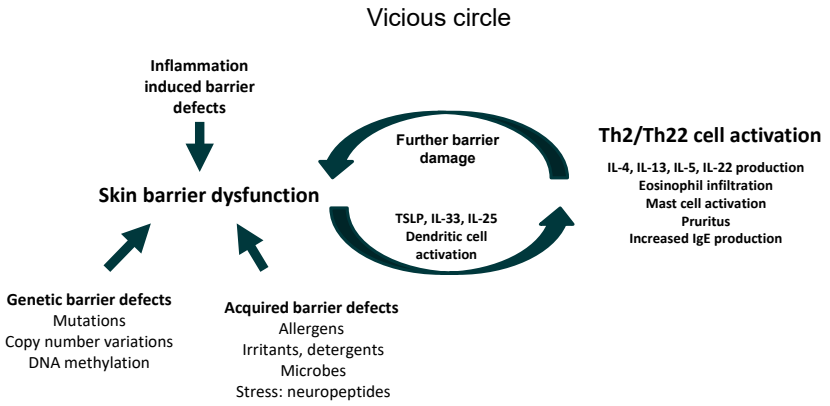
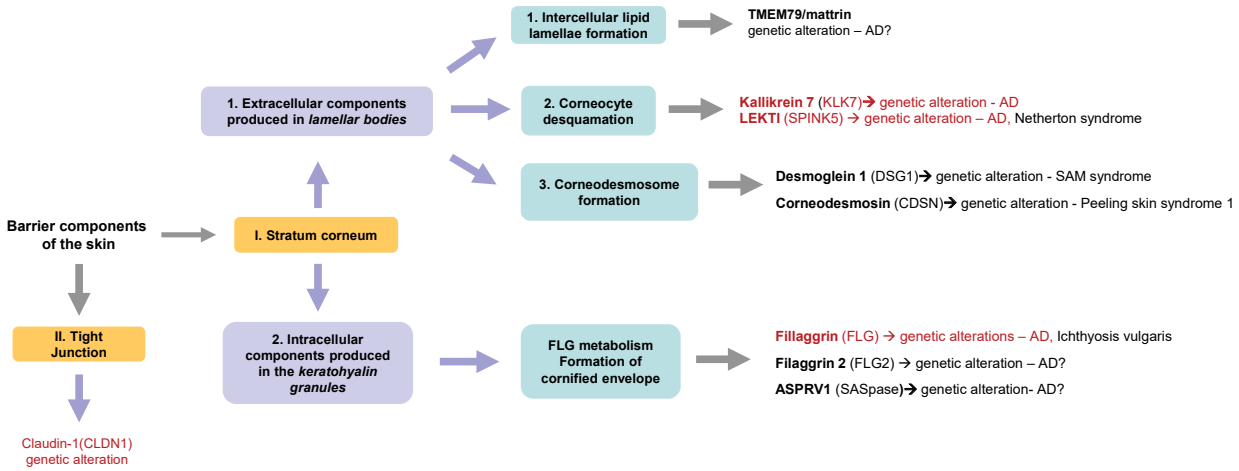


Figure 1 Pathogenesis of atopic dermatitis



- *Red letters represent genetic alterations in connection with AD*
- *Black letters represent genetic alterations in diseases with AD-like dermatitis*

Figure 2 Genetic skin barrier deficiencies in atopic dermatitis (AD) and in diseases with AD-like dermatitis

decreased FLG levels in keratinocytes are mutations in *FLG2* gene and copy number variations in the profilaggrin gene. *FLG* haploinsufficiency exhibits one of the strongest genotype–phenotype associations with the clinical and laboratory characteristics of AD. Other barrier gene mutations (KLK7, SPINK5, Claudin-1) may also predispose to AD, although the occurrence of these alterations against the background of disease development is not so clearly revealed (Figure 2).

Acquired barrier disruption and acquired FLG defects are also important risk factors for AD. They are caused by extrinsic agents (changes in pH of skin by detergents, allergens like Dermatophagoides pteronyssimus, pathogens like *Staphylococcus aureus*) and also by the local inflammatory cytokine milieu produced by Th2 and Th22 cells, invading the skin of AD patients.

Actual skin inflammation can be equally severe in those patients, who have genetic and in those patients who have acquired barrier dysfunction, and above all, these can even occur together in one patient. On the other hand literature data present that patients who carry *FLG* mutations have more persistent disease, a higher incidence of skin infections with herpes virus (eczema herpeticum), and a greater risk of multiple allergies and asthma than patients without such mutations. These clinical differences between the wild-type and mutant AD patients can be explained by the consecutive disruption of the skin barrier over the whole lifespan in patients with genetically impaired barrier (like hereditary *FLG* deficient patients), whereas acquired barrier deficiency usually fluctuates and is not continuously present. These observations strongly suggest that improvement of skin barrier is an effective management of AD, and can also help in the prevention of this disease.

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2d ATOPIC DERMATITIS: SKIN MICROBIOME AND ATOPIC DERMATITIS

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KEY MESSAGES

- Atopic dermatitis skin harbours a dysbiotic microbiome with overabundance of *Staphylococcus aureus*
- Activation of innate immunity by TLR2 ligands as being expressed by *S. aureus* converts acute Th2-mediated dermatitis into chronic cutaneous inflammation
- Colonization of the skin early in life with commensal Staphylococci is associated with a decreased risk to develop atopic dermatitis at later time points
- Decreased yields of the Gram-negative bacterium *Roseomonas mucosae* have been detected on atopic dermatitis skin
- Topical application of the non-pathogenic Gram-negative bacterium *Vitreoscilla filiformis* to atopic dermatitis skin attenuates cutaneous inflammation and induces tolerogenic immune responses

Atopic dermatitis (AD) is well known to be associated with an altered skin microbiota, particularly *Staphylococcus aureus* colonization and superinfection of lesional skin (Figure 1). Using bacterial 16S ribosomal RNA gene sequencing characterisation of the skin microbiome of pediatric AD patients revealed a tremendous loss of bacterial diversity and a significant overabundance of Staphylococci species accounting for approximately 90% of the cutaneous microbiome of acute AD flares. Further characterisation of Staphylococci spp. demonstrated that not only *S. aureus* but also *S. epidermidis* were significantly more abundant during flares. After therapy and resolution of AD, an increase in the diversity of the cutaneous microbiome could be detected. Using shotgun metagenomic analysis, it was shown later that patients with more severe AD had an overabundance of *S. aureus*, whereas *S. epidermidis* was more abundant in patients with less severe AD. Moreover, *S. aureus* strains being overrepresented in severe AD, were identified to belong to a single clade, whereas *S. epidermidis* communities found on the skin of less severe AD patients were mapped to different strains and clades. Interestingly, early colonization with commensal Staphylococci in 2-month old infants was associated with a decreased risk to develop AD at one year of life pointing to a crucial role for commensal bacteria in preventing development of AD. Whether *S. aureus* colonization can elicit AD or is a consequence of cutaneous inflammation is still an issue of debate. Recently, it has been reported that abundant *S. aureus* colonization could be detected in infants 2 months before developing AD. Investigating ADAM17$^{\Delta SOX9}$ mice harboring a dysbiotic cutaneous microbiota with overabundance of Corynebacterium spp. and *S. au-*

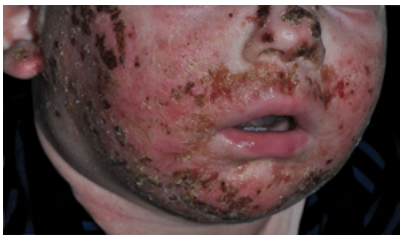

Figure 1 Severe atopic dermatitis in an infant presenting with oozing papulo-vesicles and erythema on the face covered by yellowish crusts indicating superinfection with Staphylococcus aureus

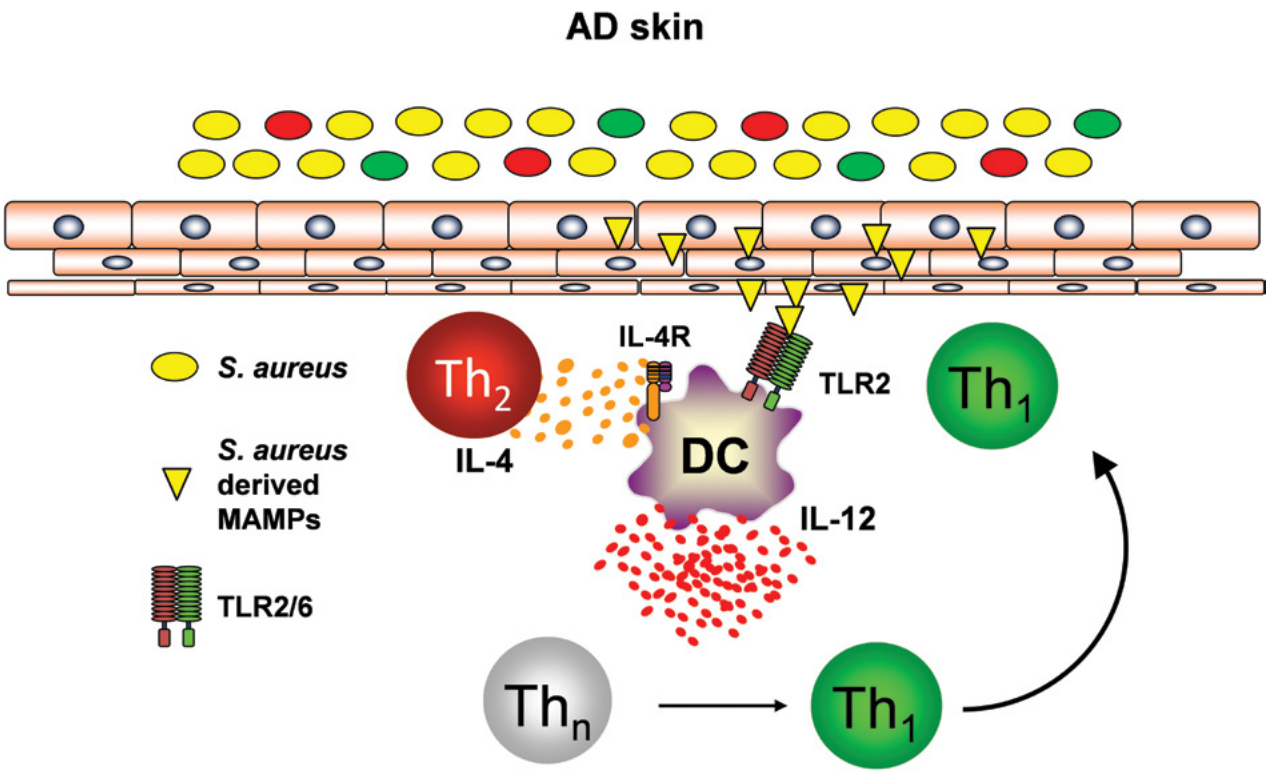

Figure 2 Dual activation of skin-resident DC by IL-4 and TLR2 ligands promotes IL-12 expression and Th1 polarization. In atopic dermatitis skin, Th2 cells secreting IL-4 are abundantly present. Skin-resident DC are activated by *S. aureus* derived TLR2 ligands (lipoproteins, lipoteichoic acid) in an IL-4 rich environment leading to DC maturation and enforced IL-12 secretion by combinatorial activation of TLR2- and IL-4R-signaling while IL-10 production is markedly attenuated. As a consequence in the local lymph nodes, naïve T helper cells are preferentially polarized into a Th1 phenotype promoting long-lasting cutaneous inflammation after homing to atopic dermatitis skin. Reproduced from (9)

reus demonstrated that *S. aureus* can drive development of eczematous lesions. In addition, activation of innate immunity in the skin by TLR2 ligands, as being present in *S. aureus*, was shown to convert acute Th2-mediated dermatitis in chronic cutaneous inflammation (Figure 2). Taken together, these data show that a dysbiotic microbiome with overabundance of *S. aureus* can act at different stages of AD development and disease course.

In addition to the undoubtful impact of Gram-positive Staphylococci in AD, a yet unknown role for Gram-negative bacteria of the cutaneous microbiota has been reported recently. AD patients harbor significantly less yields of the Gram-negative bacterium *Roseomonas mucosa*. *R. mucosa* from healthy volunteers but not from AD patients was capable of reducing *S. aureus* viability and skin inflammation in a murine AD model. In addition, innate immune sensing of the non-pathogenic Gram-negative bacterium *Vitreoscilla filiformis* has been shown to induce IL-10 producing tolerogenic dendritic cells and regulatory type 1 (Tr1) cells attenuating skin inflammation in a murine AD model after topical application (Figure 3). Thus Gram-negative bacteria have been shown to play a pivotal role in alleviating cutaneous inflammation in AD and open up the road for new therapeutic strategies.

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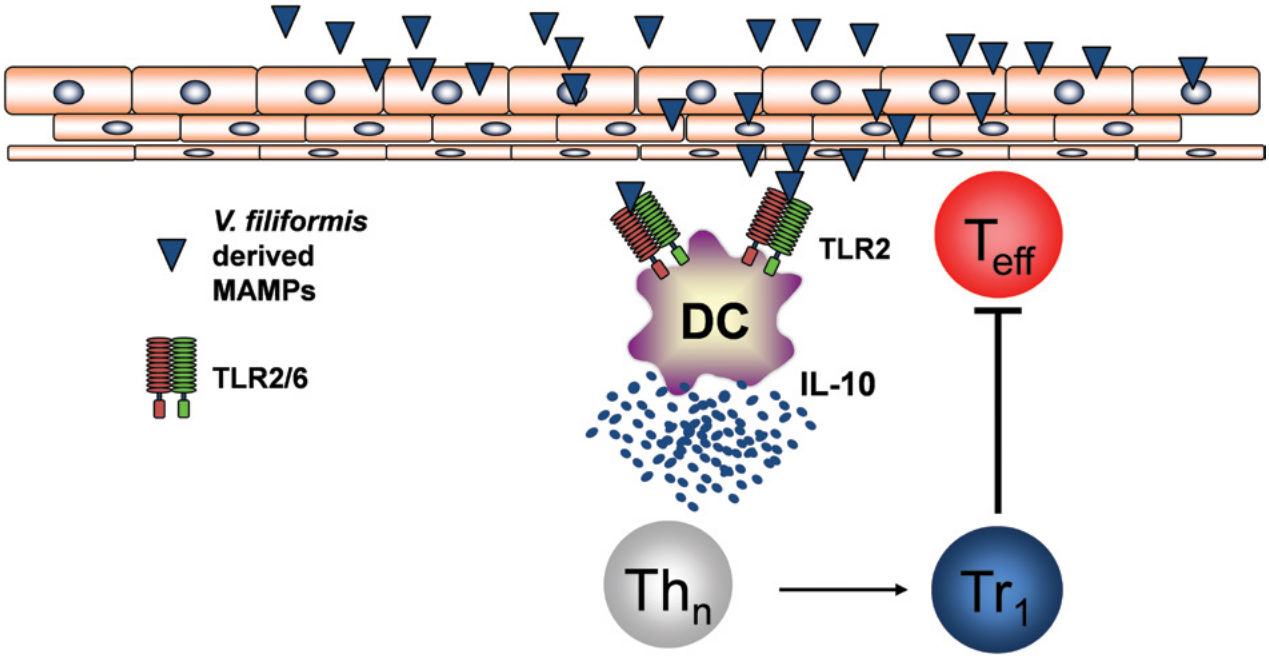

Figure 3 Non-pathogenic bacterium *V. filiformis*-derived MAMPs induce tolerogenic DC and Tr1 cells. *V. filiformis*-derived MAMPs activate DC to produce IL-10 via a TLR2-dependent mechanism. DC-derived IL-10 is required for subsequent polarization of naïve T helper cells into a Tr1 phenotype characterized by low IFN-γ and high IL-10 secretion. Vf-induced Tr1 cells efficiently block effector T cells (T_{eff}) demonstrating regulatory function leading to attenuation of skin inflammation. Reproduced from (9)

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2e ATOPIC DERMATITIS: IMMEDIATE TYPE ALLERGY AND ATOPIC DERMATITIS

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KEY MESSAGES

- Patients with atopic dermatitis (AD) have a much higher risk to develop sensitization and immediate type food allergy than individuals without AD
- Immediate type food allergy is highest in patients with early onset and severe AD
- Immediate type reactions occur often during the first feeding of the allergenic food
- Screening for sensitization to food allergens (e.g. hen's egg or peanut) that have not been introduced into the infants diet so far is helpful in patients with high risk for the development of food allergy
- Clinical relevance of sensitization should be determined (e.g. with oral food challenges)

Atopic dermatitis (AD) starts often in childhood. It has been shown that patients with AD have a high rate of sensitization especially to food allergens. Screening 2,184 infants with AD in 12 countries, 56% were sensitized to at least one allergen with highest rates for hen's egg (42%). Sensitization seems to occur mainly via the cutaneous route due to the impaired skin barrier function (see subsection 10) and AD has been recently identified as a major risk factor for the development of hens' egg sensitization in infancy. It has been shown recently that food allergens are ubiquitous in the domestic environment, increase with food consumption and can even be found in bed dust allowing a constant interaction of the skin immune system with a given allergen.

These young patients with AD have not only higher rates of sensitization to food allergens but also a much higher risk to develop immediate type allergic reactions than infants and children without AD. This has been shown on a population-based sample of 4,453 one-year-old infants from Australia. One in five infants with AD were allergic to peanut, egg white or sesame, compared to one in twenty-five infants without AD (Figure 1). It was shown that the development of food allergy was highest in infants with early onset and severe AD and over half of this children developed challenge-proven food allergy.

These immediate type reactions can affect every organ system and might be life-threatening. Patients might present most often with immediate type skin symptoms, such as urticaria (Figure 2), followed by gastrointestinal (e.g. vomiting), respiratory (e.g. wheezing) and/or cardiovascular symptoms (e.g. drop in blood pressure). The first reactions occur often at the introduction of the food into the infants diet.

Diagnostic approaches include patient history, determination of sensitization (allergen-specific IgE/skin prick test) and, if necessary, an oral provocation test. Clinical relevant food allergy in a patient with AD is very likely if a patient has a clear history of an anaphylactic reaction and sensitization to the offending food. In this case an oral food challenge should be considered at a later time to determine natural tolerance development. In patients with severe AD but without immediate

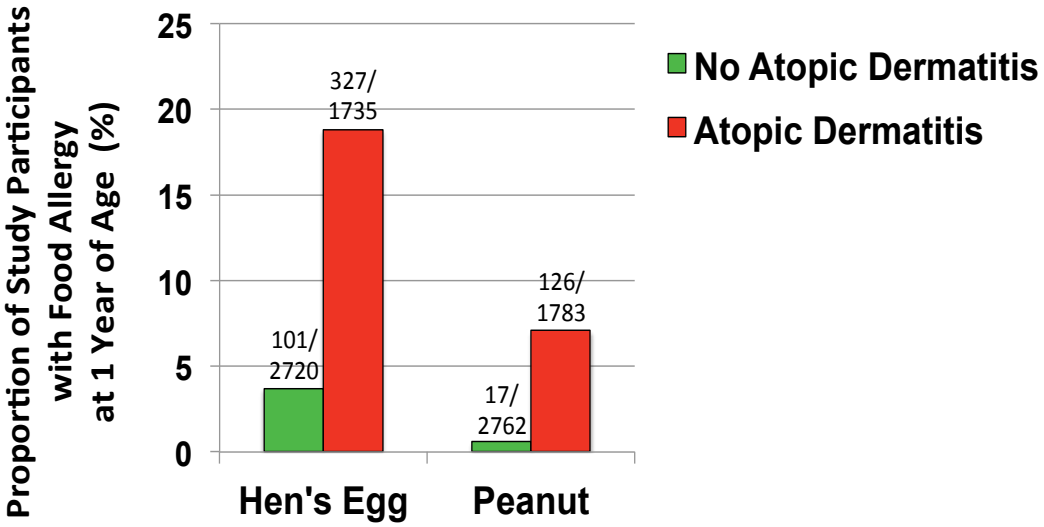

Figure 1 Hen's egg and peanut allergy in Australian children with and without atopic dermatitis. Data modified from Martin et.al

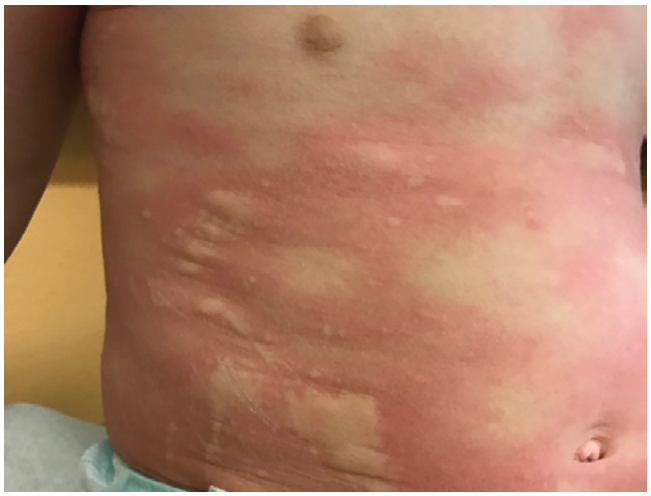

Figure 2 Urticaria is the most common immediate type symptom of food allergy in patients with atopic dermatitis. It often occurs at the first exposure of the allergenic food

type allergic reactions, food sensitization should be determined for foods that have not been introduce into the infants diet so far. In sensitized patients an oral food challenge is afterwards often necessary to determine the clinical relevance of the sensitization. The diagnostic procedure is shown for suspected peanut allergy in Figure 3 as an example.

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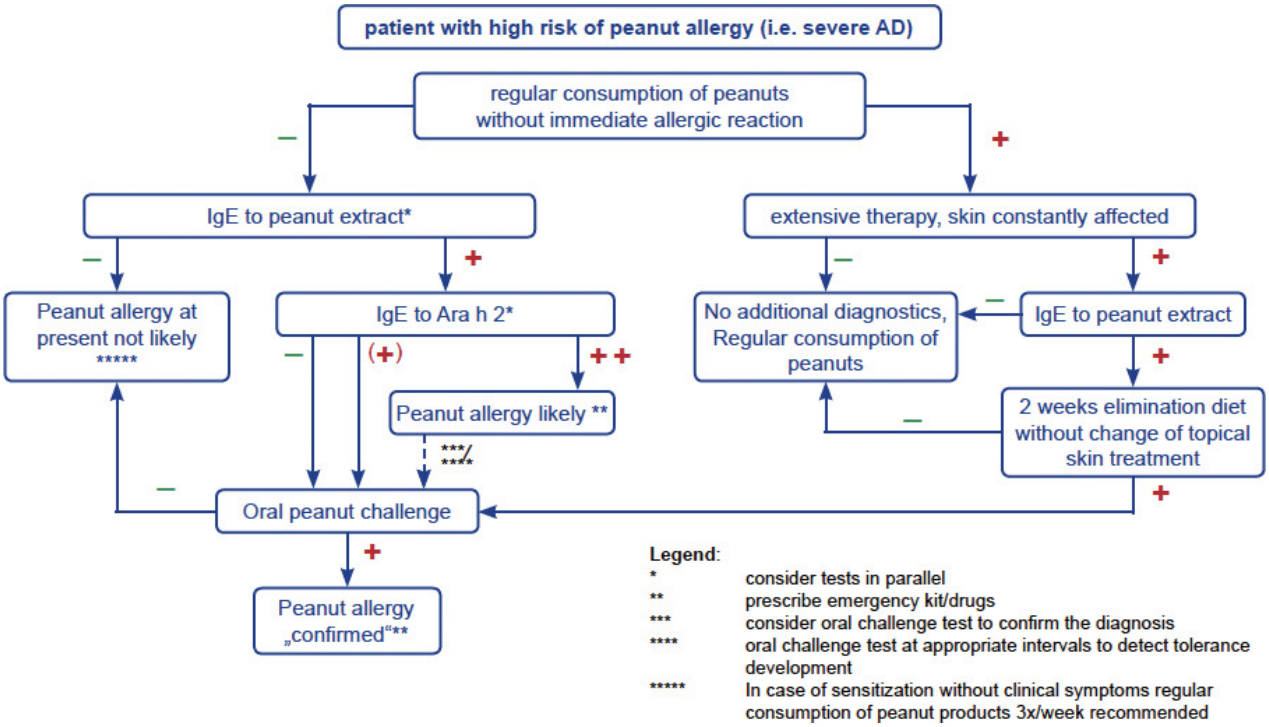

Figure 3 Patients with atopic dermatitis have a high risk for peanut allergy and sensitization might be excluded prior to the consumption of peanut-containing products. Depending on the context, the color-coded circles with plus (+) or minus ( ) carry different meanings: either positive/negative, yes/no or observed effect/no effect

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2f ATOPIC DERMATITIS: CONTACT ALLERGY AND ATOPIC DERMATITIS

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Allergic contact dermatitis (ACD) is a clinical problem in both children and adults with atopic dermatitis (AD). Although still controversial, a substantial relationship between AD and ACD is suggested. Predisposing factors proposed to contribute to the intricate immunopathogenesis linking AD and ACD are deficiencies in filaggrin, Staphylococcus aureus infection, altered pH, and vitamin D levels.

Allergic contact dermatitis is not rare in (children with) atopic dermatitis (AD). However, the role of contact allergy in AD patients is still underestimated. A 'Sherlock Holmes-like' approach is required for pinpointing the causes for some cases of eczema. The diagnosis of contact dermatitis requires a careful evaluation of a patient's clinical history, physical examination, and skin testing. The history should include all contributory factors. It is important to learn about known allergies, hobbies and leisure activities, after-school work in adolescents, topical and systemic medications used (prescribed and over the counter), use of or exposure to cosmetics and skin care products.

In a patient with atopic dermatitis a suspicion of contact dermatitis should be triggered by:

KEY MESSAGES

- Allergic contact dermatitis (ACD) is a clinical problem in both children and adults with atopic dermatitis (AD), and is not rare in children
- Use emollients. However: be aware of unwanted 'hidden' ingredients, and of the allergic potential of plant derivatives used in 'natural' herbal remedies
- Children with atopic dermatitis seem to be at greater risk of sensitization to certain allergens including components of skin care products and nickel
- A 'Sherlock Holmes-like' approach is required for pinpointing the causes for some cases of eczema
- Perform patch tests in every case of chronic recurrent or therapy-resistant eczema in children and adults
- Prevention through exposure avoidance from an early age to the most frequent contact sensitisers, especially fragrances in patients with atopic dermatitis, is very important

- Suggestive history
- Suggestive clinical distribution of skin lesions
- Severe eczema, especially if unresponsive to topical therapies
- Hand or foot eczema
- Therapy-resistant atopic dermatitis

The link between a positive patch test result or contact hypersensitivity and atopy has been studied. Patients with a personal or family history of atopy showed an increased risk of ACD, providing further evidence for the link between atopy and ACD and suggesting that children of atopic parents should avoid potential contact allergens and would likely benefit from prophylactic emollient use.

Contact sensitization may worsen the skin condition and influence the course in patients with atopic eczema. Moreover, sensitized atopic subjects may respond to very low concentrations of contact allergens because of their impaired skin barrier function and hyper-reactivity to irritant stimuli enhancing contact reactions.

Multiple studies found increased sensitization rates to various allergens among children with AD, including, among others, potassium dichromate, Compositae mix, disperse blue, balsam of Peru, fragrance mix, and lanolin. Sensitization to nickel sulfate is also commonly noted in children with AD. Allergy to nickel has been associated with a wide range of consumer products, including rivets, jewelry, belt buckles and, also more recently, cell phones and laptop computers.

Patients with AD seemed to be more likely to have a relevant positive patch tests to substances found to be relevant with exposures localizing to the skin care regimen of AD patients. Children with AD showed significant reaction patterns to allergens notable for their use in skin care preparations.

To illustrate this problem: An eleven year old boy, known with atopic dermatitis, visited our outpatient clinic having a therapy-resistant dermatitis around the mouth. Patch tests showed a positive test result after 72 hours to the lip balm he was using (Figure 1a, Figure 1b), indicating an allergic contact dermatitis to (ingredients) of this lip balm.

Emollients have been used for many years, especially in atopic dermatitis, and are considered as the mainstay of maintenance therapy. Emollients may compensate for barrier defects. However, be aware of unwanted 'hidden' ingredients. An emollient consists of a carrier, containing lipophilic (natural oils or waxes, synthetic mineral oil compounds) and/or hydrophilic (water, moisturizer, and gels) components, and other ingredients (a moisturizer, emulsifiers, and preservatives). Many of the additives are potential contact sensitizers.

Nowadays, we notice a rising trend of using 'natural' herbal remedies. Given the apparent increased awareness of the allergic potential of plant derivatives, we have to take this into account when recommending topical products.

Systematic patch testing is necessary in children with moderate-to-severe atopic dermatitis whose condition is refractory to treatment or whose history is suggestive of allergic contact dermatitis.

Atopic patients are at a significant risk of developing contact dermatitis, especially of the hands, when exposed to occupational irritant factors, that is, chemicals, water or soil. Preventive strategies should be developed and optimized to reduce the incidence of occupational dermatitis in AD patients. Furthermore, given the high exposure to the same haptens in later life, prevention through exposure avoidance from an early age to the most frequent contact sensitizers, especially fragrances in patients with atopic dermatitis, is very important. Ingredient labeling on cosmetics is important to help identifying possible allergens in products. Good information on preventing the development of ACD in children is useful for caregivers of children with atopic dermatitis.

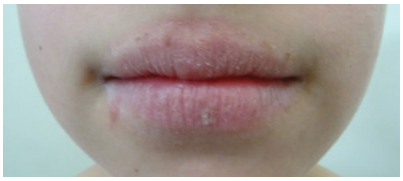

Figure 1a Eleven year old boy with therapy resistant dermatitis around the mouth

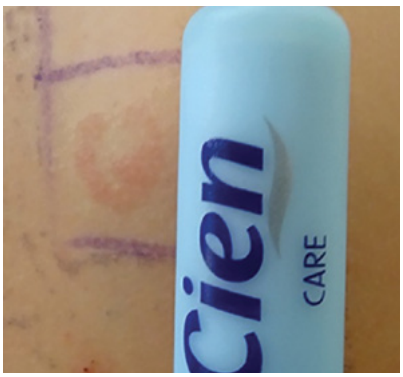

Figure 1b Positive patch test to lip balm used by eleven year old boy

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2g ATOPIC DERMATITIS: CLINICAL FEATURES OF CHILDHOOD ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a chronic or chronically-relapsing dermatitis characterized by pruritus, a typical morphology and distribution of skin lesions, and a personal or family history of atopic disease. Traditionally, the Hanifin & Rajka criteria has been used for the diagnosis of atopic dermatitis in children. However, today the validated UK working party criteria is mostly applied and are developed for different age-groups. To evaluate the severity of AD different scoring systems can be used in children such as SCORAD, PO-SCORAD or EASI.

AD typically constitute of three phases: The infantile phase from 0-2 years of age, the childhood phase between 2 and 12 years of age and the adolescent or adult phase. The typical locations during the infantile phase are the face and extensor sides of the extremities (Figure 1), whereas during childhood the flexural involvement dominates (Figure 2). The skin lesions in adolescents and adults more frequently involve the hands, head and neck. However, the localization and extent varies considerably and there is some overlap between age groups. The dermatitis may be acute or chron-

KEY MESSAGES

- Atopic dermatitis typically begins during infancy or early childhood
- It is a chronic or chronically-relapsing dermatitis characterized by pruritus, a typical morphology and distribution of skin lesions, and a personal or family history of atopic disease such as asthma and allergic rhinoconjunctivitis
- The locations in infancy typically are the face and extensor sides of the extremities while in childhood the flexural involvement is characteristic

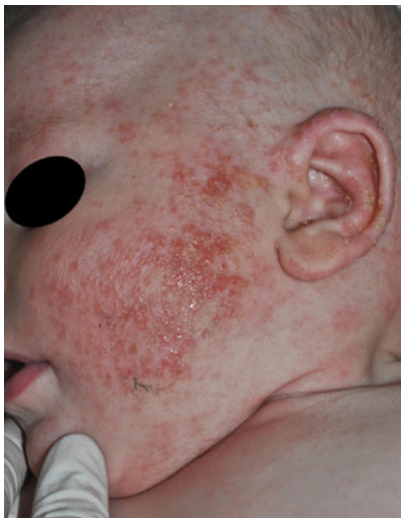

Figure 1 Acute atopic dermatitis in an infant. Non-sharply demarcated erythema, papules, vesicles, oozing, crusting can be seen

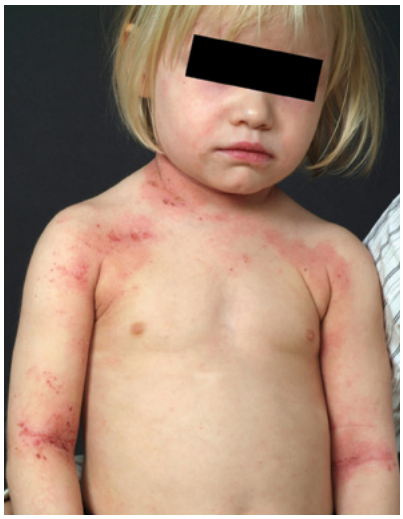

Figure 2 Subacute atopic dermatitis in childhood. Flexural lesions dominate and some thickening of the skin develops in involved areas

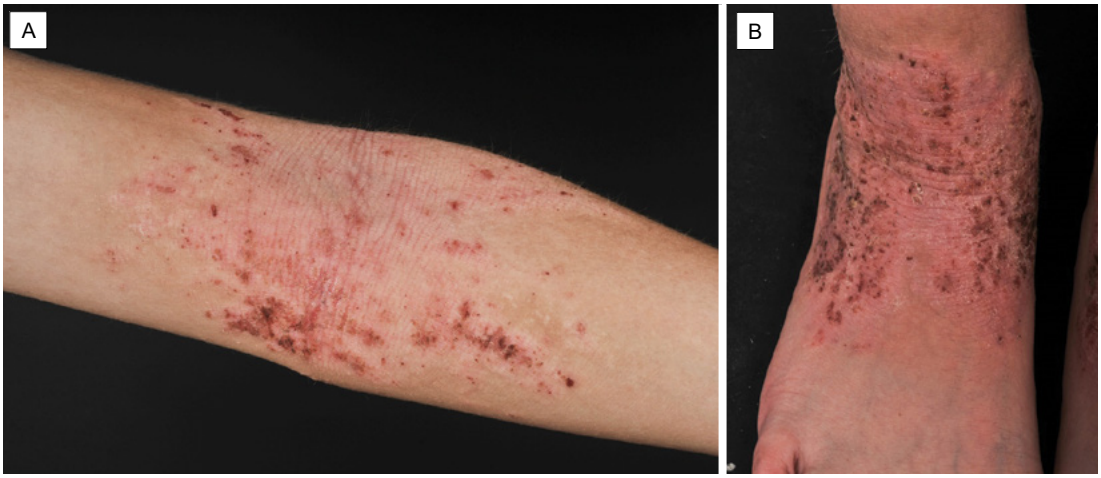

Figure 3 Chronic atopic dermatitis in adolescence shows thickened plaques with strong lichenification (a+b)

ic. Acute lesions predominate in infantile AD and are characterized by intensively itching, erythema papules, vesicles, oozing, crusting and often excoriations. Chronic lesions, which typify later childhood AD show thickened plaques with lichenification (Figure 3). A cardinal feature is xerosis – meaning persistently dry, scaly skin in a generalized distribution, which is caused by the impaired skin barrier function including loss-of-function mutations in the filaggrin gene. A main feature of AD is itching and children with AD often have troubles with sleeping due to itching. Associated clinical features ("stigmata") are Dennie-Morgan lines (prominent horizontal folds under the lower eyelids), palmoplantar hyperlinearity, pityriasis alba (white spots), white dermographism (white streaks after stroking) and cheilitis. Concomitant ichthyosis vulgaris and keratosis pilaris can be seen.

Among children with AD less than 6 years of age around 15-30% have a concomitant food allergy which in selected cases also may exacerbate the eczema. Furthermore, comorbidity in form of asthma and allergic rhinitis may develop in childhood and adolescence. Allergic contact dermatitis is also found in childhood atopic dermatitis and should be suspected in moderate to severe cases not responding to treatment, with unusual location of the atopic dermatitis and in children with hand eczema.

Complicating and exacerbating factors in AD further include infections with *Stapholycoccus aureus* (impetigo), poxvirus (molluscum contagiosum), *Herpes simplex virus* (eczema herpeticum), and *Malassezia furfur* (adolescents). Furthermore, environmental factors such as irritants may exacerbate the dermatitis.

The diagnosis may sometimes be challenging and atopic dermatitis may resemble other types of dermatitis as well as other skin diseases such as psoriasis, infections, infestations and malignancies as well as metabolic, genetic and autoimmune disorders.

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2h ATOPIC DERMATITIS: CLINICAL FEATURES OF ADULT ATOPIC DERMATITIS

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Adult atopic dermatitis (AD) can be differentiated into two main disease courses: 1) a continuation of childhood-onset AD; 2) onset during adulthood (late-onset).

When AD is diagnosed in infancy or childhood - the continuation of the disease into adulthood often resembles the predilection sites and severity seen during childhood (refer to Chapter E2g). In case of adult onset of atopic dermatitis - the typical symptoms may be absent and predilection sites for eczema differ. Flexural eczema is less frequently seen in late-onset AD and more often may affect the trunk as well as extensor skin areas on the extremities. Prurigo nodules and nummular skin lesions occur more frequently in adult-onset AD. Allergic rhinitis (with its consequences), as well as a positive history of food allergy and asthma, are less often associated with the late-onset AD and one-third of these patients have negative history towards these symptoms.

Adult-onset atopic dermatitis occurs in the 3rd - 5th decade of life and it commonly presents with face-, hand- or generalised-dermatitis. The classic AD signs (i.e. Hertoghe sign, Dennie–Morgan infraorbital fold white dermographism, nipple eczema or orbital darkening) may, or may not be present in adult-onset AD. Pruritus on the other hand, with multiple eczematous lesions, is a *sine qua non* criterium (Figure 1). Table 1 illustrates differences in clinical features of the adult- and childhood-onset AD.

KEY MESSAGES

- Adult atopic dermatitis (AD) can be a continuation of childhood-onset AD or can first occur in adulthood (late-onset)
- Late-onset AD is more heterogeneous in its clinical presentation and is more frequently associated with normal IgE levels
- Specific diagnosing criteria for late-onset AD do not exist

The disease severity, however, does not differ in both adult-onset and childhood-onset-AD as measured by EASI, SCORAD, POEM or QoL questionnaires. Differences in clinical features of adult onset-AD may be related to the fact that these patients very rarely present filaggrin loss-of-function mutations. Additionally, late-onset AD is more frequently associated with low IgE levels and no detectable sensitizations against aero- and food-allergens. This correlates with the lower predisposition to atopic comorbidities and would in part explain the differences in clinical presentation.

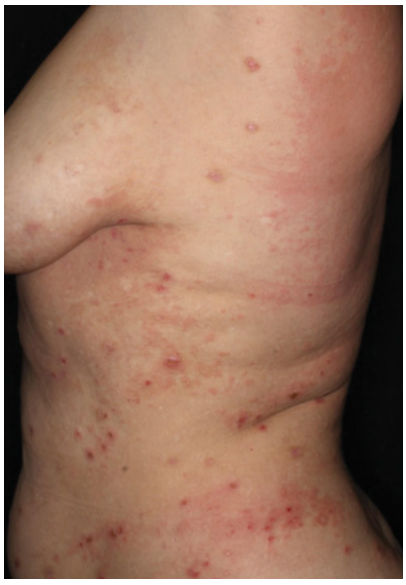

Figure 1 Typical skin lesions in late-onset atopic dermatitis. Please notice the presence of erythematous plaques and multiple disseminated papules with excoriations

TABLE 1

Symptoms of childhood and adult-onset AD		
	similarly common	less common in adult-onset AD
Concomitant diseases:	medication allergy	asthma
		allergic rhinitis
		food allergy
Symptoms:	xerosis	flexural dermatitis
	pruritus	neck-fold dermatitis
		eye-lid dermatitis
		cheilitis
		pityriasis alba
		scalp involvement
Signs:	pruritus when sweating	cutaneous infections tendency
	white dermographism	palmar hyperlinearity

Due to the lack of specific diagnostic criteria for the diagnosis of late-onset AD, Hanifin & Rajka criteria are still considered the gold standard. Although, they were originally designed for the childhood-onset AD and their specificity and sensitivity in diagnosing adult-onset AD may be lacking. Clinicians have to be aware that the adult-onset AD is more heterogeneous and confidently make the diagnosis when the clinical presentation resembles AD and other etiologies are excluded. This is especially important in cases when IgE values are normal and atopic features are missing.

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2i ATOPIC DERMATITIS: SPECIAL FORMS OF ATOPIC DERMATITIS

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Atopic dermatitis is commonly presented with recurrent itchy dermatitis in typical age-related distribution, in association with dry skin (Figure 1). The best summary of symptoms and objective signs of the disease is found in the criteria by Hanifin and Rajka. The clinical appearance is however sometimes more complex, with special and atypical presentations/forms not included in the Hanifin and Rajka criteria (e.g. atopic winter feet and earlobe rhagades).

The atypical clinical presentation can either be site-specific or have morphological characteristics (Table 1). The morphological variants are often clinically notable and some have certain sites of location, such as ear, eyelids, nipples, fingers and feet. These special or minimal forms of atopic dermatitis may occur alone, together or alternate with more typical clinical presentations.

Sharply demarcated patches and plaques of inflamed skin are characteristic of nummular or discoid eczema, and are very often secondarily infected with S. aureus. The extremities and buttocks are the most commonly affected areas, and this variant is often very difficult to treat.

KEY MESSAGES

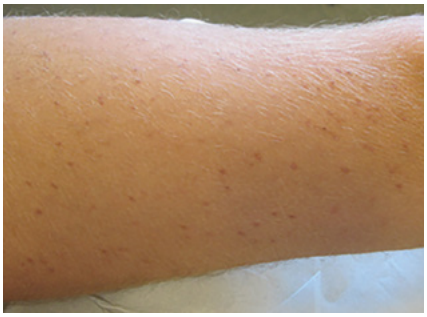
- Atopic dermatitis is a chronic relapsing skin disease with many different clinical presentations that may vary
- Different disposition, exposure, age and ethnicity may result in less common and special forms of atopic dermatitis
- Knowledge of the minimal and special forms of atopic dermatitis together with diagnostic criteria is a prerequisite for the correct diagnosis

Patchy pityriasiform lichenoid eczema is a dry and only somewhat itching follicular type of atopic dermatitis common in Japanese patients. This variant is characterized by plaque-shaped, lichenoid, scaly eczema and skin-coloured follicular papules, mainly on the lateral sides of the trunk.

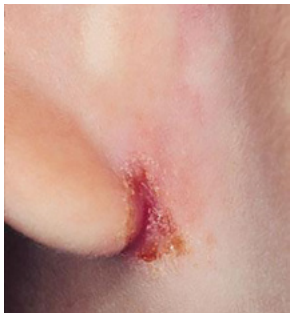
Another variant of atopic dermatitis is juvenile papular dermatitis characterised by lichenoid flat papules often hypopigmented. It is localized mainly on the elbows and knees and is thought to be associated with pollinosis as it primarily occurs in the spring and summer.

TABLE 1

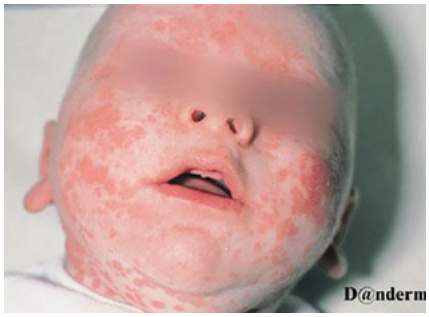
Special and minimal forms of atopic dermatitis	
Special forms of atopic dermatitis	**Minimal forms of atopic dermatitis**
Nummular type atopic dermatitis	Atopic feet (“atopic winter feet”)
Follicular atopic dermatitis	Atopic hands and atopic finger pad eczema
Psoriasiform atopic dermatitis	Ear eczema (earlobe rhagades or retroauricular)
Papular atopic dermatitis	Cheilitis (perioral or exfoliating)
Juvenile plantar dermatosis	Nipple eczema
	Genital eczema



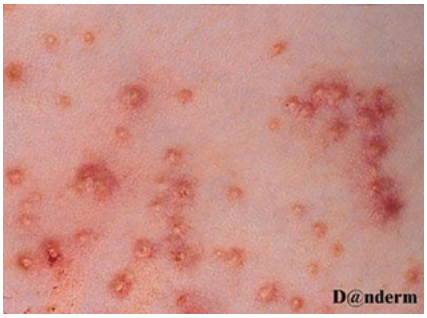
Papular atopic dermatitis



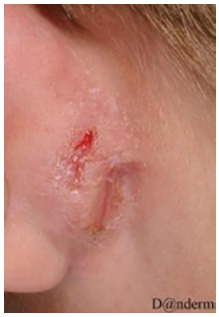
Infected fissure on the earlobe



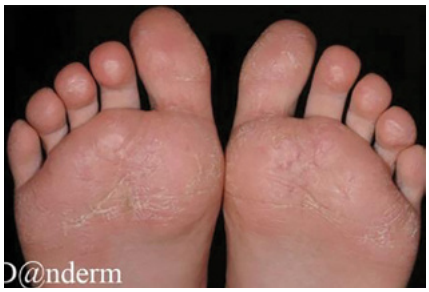
Psoriasiform dermatitis



Pityriasiform (follicular type) of atopic dermatitis



Retroauricular fissure



Atopic winter feet in a child

Figure 1 Examples on clinical presentation of special and minimal forms of atopic dermatitis. (*The authors would like to acknowledge Professor Niels Veien from Aalborg, Denmark for permission to use the clinical pictures from his online database, Danderm*)

Psoriasiform atopic dermatitis is considered to be an overlap between atopic dermatitis and psoriasis which often involves the scalp or diaper area. Most frequently diagnosed in asian children and often with resistant to topical treatment.

Patients of colour and other patients with dark skin often suffer from a papulonodular form of AD with post-inflammatory hyperpigmentation.

The knowledge of manifestations and clinical variations in the special and minimal forms of atopic dermatitis might provide helpful tools in diagnosing early or rare cases of atopic dermatitis.

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2j

ATOPIC DERMATITIS: INFECTIOUS COMPLICATIONS OF ATOPIC ECZEMA (AE)

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KEY MESSAGES

- Bacterial and viral infections are common complications of atopic eczema
- The most important bacterial infection is impetiginisation with Staph. aureus
- The most important viral infection is eczema herpeticum as it can lead to severe complications such as herpetic keratitis, herpetic meningitis or encephalitis. Therefore prompt initiation of systemic antiviral therapy is crucial

Patients with AE are predisposed to develop skin infections because of an impaired skin barrier and modified immunity.

Bacterial infections are most frequently caused by Staphylococcus aureus, but Streptococus pyogenes infection is also possible. Colonization with S. aureus is common in AE. To diagnose impetiginization, there must be clinical signs such as weeping, yellow crusts or small superficial pustules (Figure 1a). Furuncles, abscesses, erysipelas and systemic signs of infection such as fever and leukocytosis are rather uncommon. If skin involvement is limited, topical therapy (eg fusaric acid) can be used, whereas oral antibiotic therapy is recommended for patients with widespread lesions.

Frequent viral infections in AE are eczema herpeticum, eczema molluscatum and eczema coxsackium (Table 1).

Eczema herpeticum, the most common viral infection in AE, is caused by Herpes simplex virus type 1 or 2. It can present initially as an eruption of umbilicated vesicles, but often there are multiple monomorphic, punched-out erosions with hemorrhagic crusts (Figure 1b). Eczema herpeticum can present at any site, with a predilection for the head, neck and trunk. Association with fever, reduced general condition and lymphadenopathies is common. Complications are herpetic keratoconjunctivitis and viremia, which can lead to meningitis and encephalitis. Secondary bacterial infection is possible.

Diagnosis is made on clinical presentation and can be confirmed by several techniques (viral culture, polymerase chain reaction testing, immunofluorescence, Tzanck test). In case of periocular lesions an ophthalmologist should check for herpetic keratitis.

Prompt start of systemic antiviral therapy (aciclovir or valaciclovir) is crucial to limit disease duration and prevent complications. Patients with herpetic conjunctivitis should receive combined systemic and topical antiviral therapy. Topical therapy with antiseptic lotions is recommended to dry out the vesicles and to prevent bacterial superinfection.

ECZEMA MOLLUSCATUM

Mollusca contagiosa are caused by a poxvirus and present clinically as umbilicated, small, skin-colored papules (Figure 1c). Patients with AE have more widespread disease than nonatopic individuals, sometimes with hundreds of lesions. The mollusca are most frequently localised in eczematous lesions, but can spread to non-eczematous skin due to autoinoculation. The general condition is good and there are no internal complications.

TABLE 1

Clinical features, diagnosis, complications and management of the most common infectious complications of atopic eczema

Atopic eczema complication	Infectious agent	Clinical presentation	Diagnosis	Possible Complications	Therapy
Impetiginization	*Staphylococcus aureus*	weeping, yellow crusts, small superficial pustules	Clinical presentation, bacterial swab	Systemic infections rare	Topical or systemic antibiotics
Eczema herpeticum	Herpes simplex type 1/2	umbilicated vesicles or multipel monomorphic, punched-out erosions with hemorrhagic crusting	Clinical presentation, various techniques (culture, PCR, Tzanck test)	Herpes keratitis; Meningitis, encephalitis	Systemic antiviral therapy
Eczema molluscatum	Molluscum contagiosum virus	umbilicated, small, skin-colored papules	Clinical presentation; (histopathology)	Self limiting	Local destruction
Eczema coxsackium	Enteroviruses	papulovesicular lesions or hemorrhagic and crusted lesions	Clinical presentation; Exclude herpes simplex infection (see above)	Self limiting	Emollient; topical corticosteroids

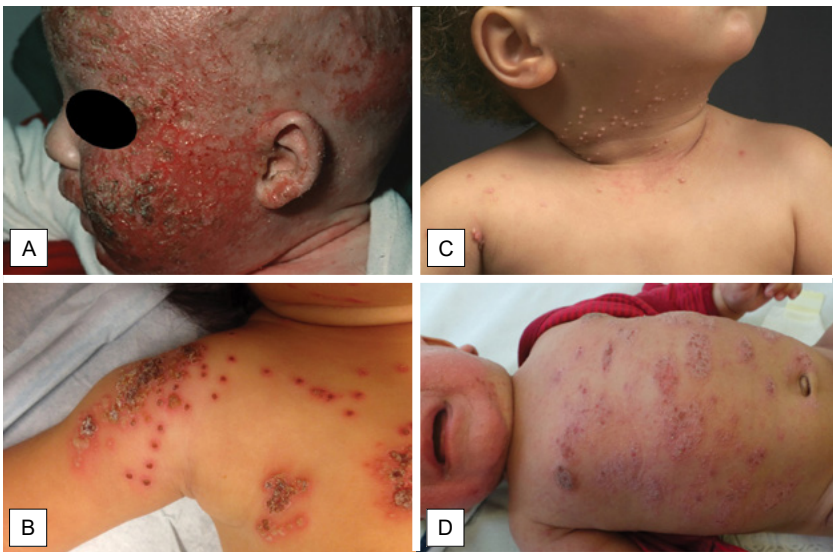

Figure 1 Most common infectious complications of atopic eczema: A: impetiginization of eczema; B : eczema herpeticum; C: eczema molluscatum; D: eczema coxsackium

Diagnosis is made on clinical presentation. In case of doubt histopathology can confirm the diagnosis. Therapy is done by local destruction (curettage, cryotherapy).

Eczema coxsackium is caused by viruses of the enterovirus group, frequently coxsackievirus A6. Clinical presentation is variable with erythematous papulovesicular lesions or hemorrhagic and crusted lesions (Figure 1d). Lesions are predominantly in areas affected by AE. Systemic symptoms such as fever usually subside in a few days. The most important differential diagnosis of eczema coxsackium is eczema herpeticum. Lesional PCR for enterovirus may be considered. Treatment is symptomatic with moisturizing creams and topical corticosteroids.

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2k ATOPIC DERMATITIS: GENETIC DISEASES RESEMBLING ATOPIC DERMATITIS

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Atopic dermatitis (AD) is the most common chronic skin disease in children, typically presenting in early infancy. AD is a chronic, relapsing, highly pruritic skin condition resulting from disruption of the epithelial barrier and associated immune dysregulation in the skin of genetically predisposed hosts. Diagnosis is based on pruritus, typical morphology and chronic course of dermatitis. Common features as pruritus, erythema and excoriations are also typical for several other inborn errors of immunity (IEI) resembling AD that can mimic, coexist with, or complicate AD: In the following a selection of four out of several genetic entities are described.

KEY MESSAGES

- Atopic dermatitis (AD) is the most common chronic skin disease in early childhood
- Common features of AD such as pruritus, erythema and excoriations are also typical for several other inborn errors of immunity
- Hyper IgE Syndromes comprise a group of rare primary immunodeficiency disorders characterized by a trias of elevated IgE levels, rash, and recurrent skin and lung infections
- Netherton Syndrome is an autosomal recessive form of congenital ichthyosiform erythroderma, scaling, trichorrhexis invaginata and other hair shaft anomalies
- Omenn syndrome is a phenotype of severe combined immunodeficiency (SCID) caused by hypomorphic mutations of several classical SCID genes such as recombinase activating genes RAG1 and RAG2
- Wiskott-Aldrich Syndrome is a X-linked recessive IEI resulting from variants in the WAS gene, characterized by immunodeficiency, eczema, thrombocytopenia, and predisposition to lymphohematopoietic malignancy

HYPER IgE SYNDROMES (HIES)

HIES comprise a group of rare primary immunodeficiency disorders characterised by a trias of elevated IgE levels, rash, and recurrent skin and lung infections (Figure 1). Autosomal dominant HIES is the prototype of these disorders, results from a mutation in signal transducer and activator of transcription-3 (STAT3) and has a variety of connective tissue and skeletal abnormalities. Several other genetically characterized immunodeficiency disorders have been identified including autosomal recessive mutations in the dedicator of cytokinesis 8 (DOCK8) and others. The associated cutaneous symptoms in STAT3 mutations begin as a pustular rash on the face or scalp at or just after birth, Patients with DOCK8 deficiency tend to develop eczematous dermatoses early after birth. Treatment has relied on prophylactic and therapeutic antimicrobials

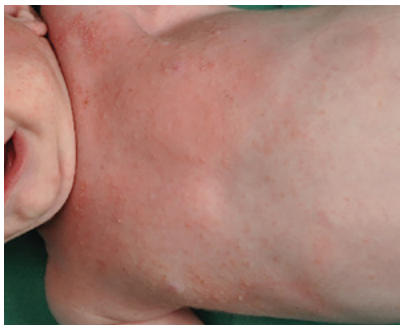

Figure 1 Child with hyper IgE syndrome, skin affection on the thorax

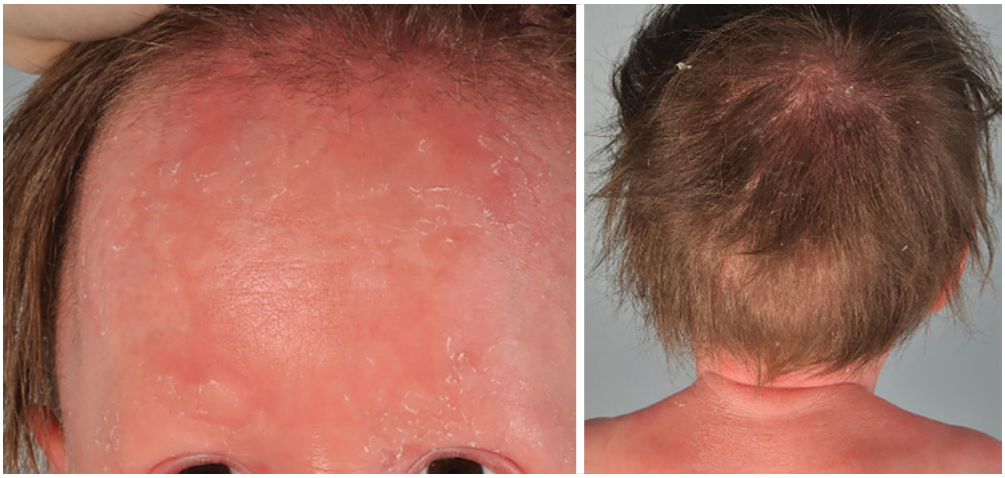

Figure 2 Forehead and hair of a child with Netherton syndrome

and aggressive skin care. Hematopoeitic allogeneic stem cell transplantation (HSCT) for STAT3 HIES is experimental, but is standard of care for DOCK8 HIES.

NETHERTON SYNDROME (NS)

NS is an autosomal recessive form of congenital ichthyosiform erythroderma, scaling, trichorrhexis invaginata and other hair shaft anomalies (Figure 2). Most patients develop a pruritic eczematous rash being poorly responsive to treatment. Later, erythroderma may be replaced by an annular and polycyclic pattern of lesions (ichthyosis linearis circumflexa). The large majority of NS patients develop atopic manifestations including asthma, and food allergy. Frequent complications include hypernatremic dehydration, recurrent life threatening infections, diarrhea and intestinal malabsorption.

NS is caused by SPINK5 mutations, which lead to absent or reduced expression of the serine protease inhibitor lympho-epithelial Kazal-type inhibitor (LEKTI). The presence of "bamboo hair" (trichorrhexis invaginata) with dermatoscopy is diagnostic. The treatment is symptomatic, often difficult, and should be tailored to the patient's specific needs.

OMENN SYNDROME

Omenn syndrome (OS) is a particular phenotype of severe combined immunodeficiency (SCID) caused by hypomorphic mutations of several classical SCID genes such as recombinase activating genes RAG1 and RAG2. OS is characterized by the presence of generalized severe erythroderma (Figure 3), hepatosplenomegaly, eosinophilia and profound immunodeficiency. Concerning the skin, eruptions and alopecia occur. OS is fatal if untreated and therefore prophylactic and therapeutic antimicrobials, immunoglobulin replacement, protection from infectious agents such as CMV are crucial in the setting of mandatory allogeneic HSCT.

WISKOTT-ALDRICH SYNDROM (WAS)

WAS is a X-linked recessive IEI resulting from variants in the WAS gene, characterized by immunodeficiency, eczema, thrombocytopenia, and predisposition to lymphohematopoietic malignancy. The first clinical sign of WAS is often bleeding-related, however eczematous dermatitis generally develops within the first few months of life (Figure 4) and is indistinguishable from AD including in its anatomical distribution. WAS-related dermatitis is pruritic and

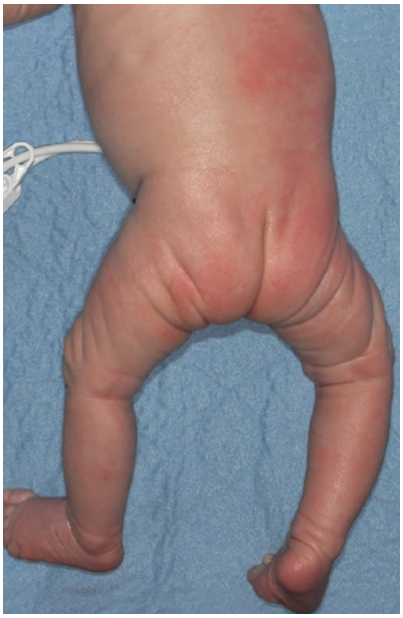

Figure 3 Back of a child with Omenn syndrome

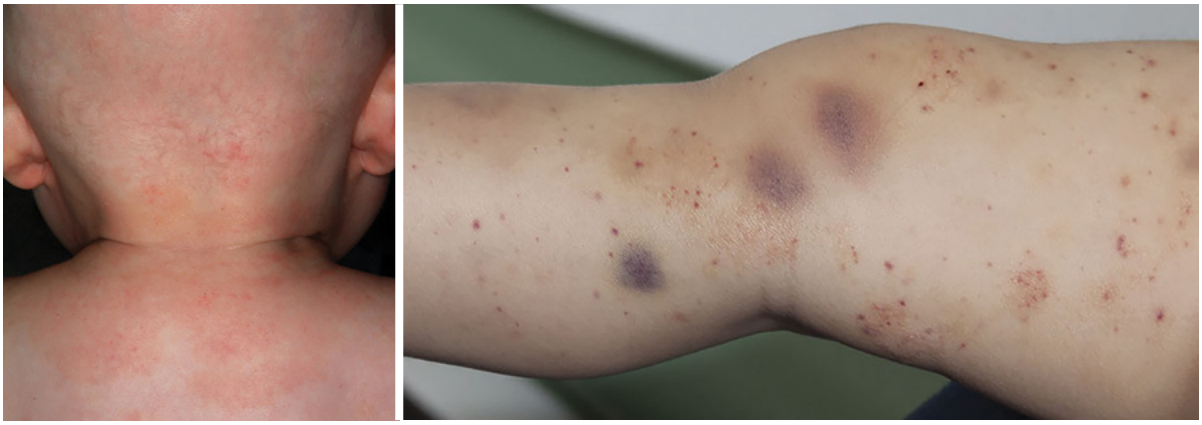

Figure 4 Patient's back of the head and leg with WAS

often improves with age. Patients are also prone to atopy. Without appropriate care and intervention, morbidity and mortality are frequent during childhood due to infection, bleeding, and malignancy. Supportive immunological care is mandatory and allogeneic HSCT or autologous gene replacement therapy should be performed early on in most of the cases.

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21

ATOPIC DERMATITIS: DIAGNOSIS OF ATOPIC DERMATITIS

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What's in a name? Strictly speaking, the term "atopic dermatitis" (AD) and its synonym atopic eczema should only be used to denote individuals with the eczema phenotype who are also atopic ie evidence of IgE-mediated allergy to common environmental allergens determined by skin prick, aeroallergen patch or blood tests (Figure 1). However, the term AD is used more loosely to denote a clinical constellation of characteristic symptoms such as itch, plus signs such as poorly demarcated erythema with surface change in typical locations such as flexures, and dry skin (xerosis).

Clinical features and diagnostic tests: Clinical features such as flexural vs non-flexural patterns of AD and tendency to skin thickening (lichenification) vary considerably by age and world region. Acute AD (erythema and exudation) also looks different to chronic thickened AD. The reference standard for diagnosis remains a clinical one. Diagnostic tests are only useful to identify those at higher risk of severe disease, food allergy, allergic rhinitis and asthma eg by determining atopy status or filaggrin gene mutations.

KEY MESSAGES

- Atopic dermatitis is a difficult disease to define because of its fluctuating nature, varying morphology and varying distribution according to age and skin type
- Non-allergic factors may be just as important in "atopic" dermatitis as allergic factors, especially at a population level
- Consensus-based criteria are fine for guiding clinical diagnosis, but criteria of known validity, repeatability and applicability are needed for scientific studies
- The UK refinement of Hanifin and Rajka's criteria have performed well in defining a stable phenotype for atopic dermatitis
- Diagnosis of adult-onset atopic dermatitis requires further research
- What is described as atopic dermatitis today is probably a manifestation of several overlapping conditions with a common appearance

Diagnostic criteria: Most diagnostic criteria such as the original Hanifin and Rajka criteria and those suggested by dermatology associations in America, Japan and Korea have been consensus-based. These long lists of major and minor criteria are perfectly appropriate for guiding diagnosis in clinical practice in their respective countries. However, they are less suitable for scientific studies that compare groups of people because of their lack of precise definitions, validity, repeatability and applicability to a range of ages and ethnicities. The UK refinement of the Hanifin and Rajka criteria are a minimum list of reliable criteria of known validity that have been widely used in research (Figure 2, Figure 3). Symptom-based questionnaire such as those used by the International Study of Asthma and Allergies in Childhood (ISAAC) have enabled global comparisons to be made (Figure 4). It is unclear how diagnostic criteria derived mainly from children perform in the diagnosis of adult-onset AD.

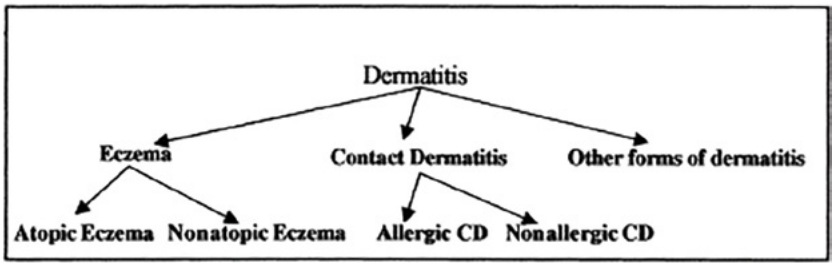

Figure 1 World Allergy Organisation nomenclature for dermatitis and eczema using correct terms to separate atopic from non-atopic disease (*Reproduced from Journal of Allergy and Clinical Immunology, Johansson SGO, Bieber T, Dahl R, et al, 113, 832-836, Copyright 2003 with permission from Elsevier*)

In order to qualify as a case of atopic eczema with the UK diagnostic criteria, the person:

Must have:

An itchy skin condition in the last 12 months

Plus three or more of:

Onset below age 2*

History of flexural involvement

History of a generally dry skin

Personal history of other atopic disease**

visible flexural dermatitis as per photographic protocol

* not used in children under 4 years

** in children aged under 4 years,history of atopic disease in a first degree relative may be included

Figure 2 The UK refinement of the Hanifin and Rajka diagnostic criteria for atopic dermatitis (taken from the free online manual https://www.nottingham.ac.uk/research/groups/cebd/resources/uk-diagnostic-criteria-for-atopic-dermatitis.aspx, accessed 21st December 2018)

Various algorithms have been derived for making a diagnosis of AD using routine data sources. The choice of diagnostic criteria will depend on their purpose. Consensus criteria are fine for clinical work, criteria with a good trade-off between sensitivity and specificity are needed for epidemiological comparisons and very specific criteria are needed to denote clinical trial populations. Further discoveries including markers of skin barrier defects (filaggrin mutations), T-helper cell immune dysregulation, and skin microbiome alterations, are likely to further stratify the clinical syndrome of atopic dermatitis into distinct subtypes with different or overlapping aetiologies, disease trajectories and response to treatment.

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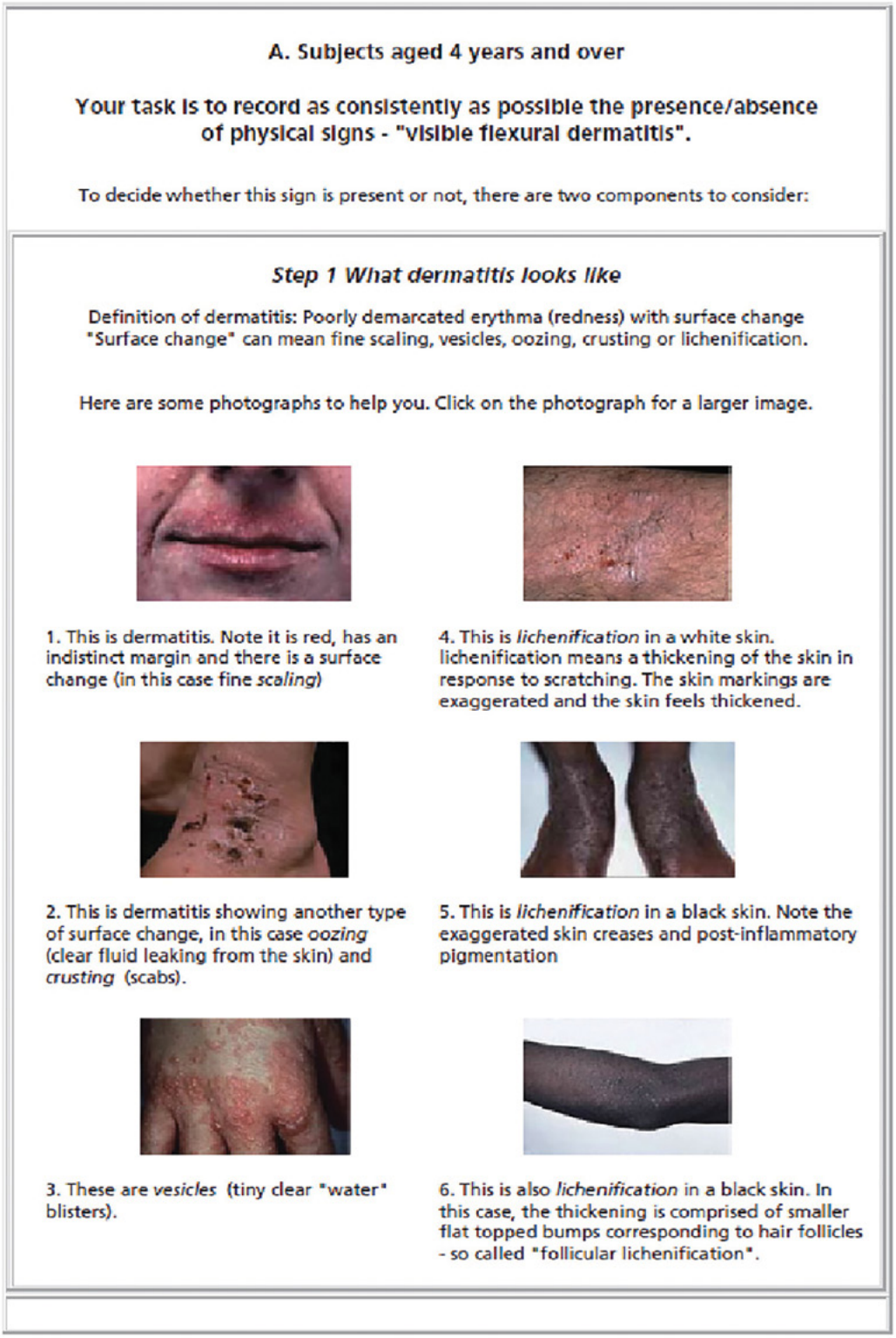

A. Subjects aged 4 years and over

Your task is to record as consistently as possible the presence/absence of physical signs - "visible flexural dermatitis".

To decide whether this sign is present or not, there are two components to consider:

Step 1 What dermatitis looks like

Definition of dermatitis: Poorly demarcated erythma (redness) with surface change "Surface change" can mean fine scaling, vesicles, oozing, crusting or lichenification.

Here are some photographs to help you. Click on the photograph for a larger image.

1. This is dermatitis. Note it is red, has an indistinct margin and there is a surface change (in this case fine *scaling*)

4. This is *lichenification* in a white skin. lichenification means a thickening of the skin in response to scratching. The skin markings are exaggerated and the skin feels thickened.

2. This is dermatitis showing another type of surface change, in this case *oozing* (clear fluid leaking from the skin) and *crusting* (scabs).

5. This is *lichenification* in a black skin. Note the exaggerated skin creases and post-inflammatory pigmentation

3. These are *vesicles* (tiny clear "water" blisters).

6. This is also *lichenification* in a black skin. In this case, the thickening is comprised of smaller flat topped bumps corresponding to hair follicles - so called "follicular lichenification".

Figure 3 Extract from the UK Working Party's protocol for recording visible flexural eczema dermatitis (taken from the free online manual https://www.nottingham.ac.uk/research/groups/cebd/resources/uk-diagnostic-criteria-for-atopic-dermatitis.aspx, accessed 21st December 2018)

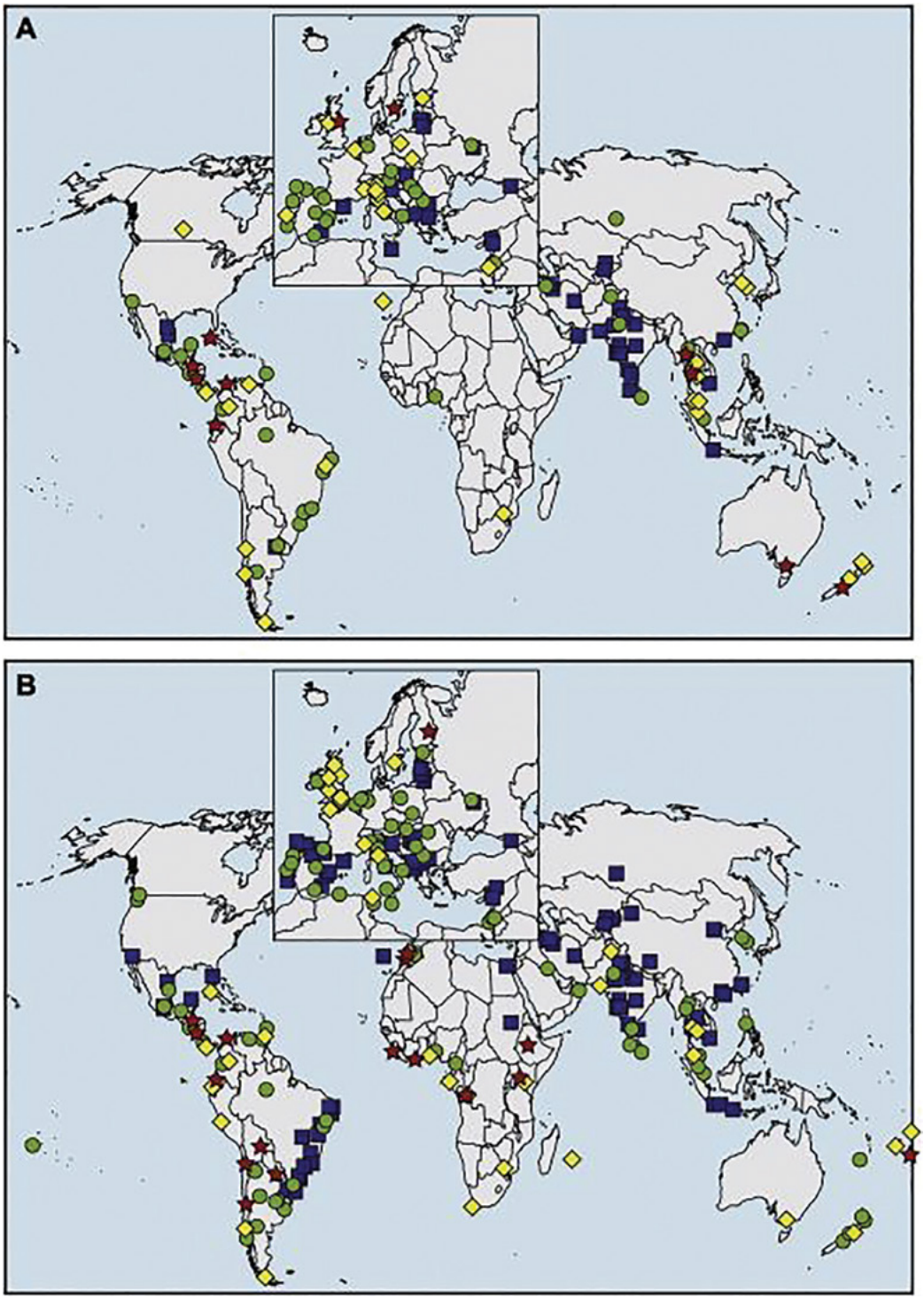

Figure 4 World maps from the International Study of Asthma and Allergies in Childhood Study showing prevalence of current symptoms of eczema for the age group 6 to 7 years (A) and 13 to 14 years (B). Each *symbol* represents a center. *Blue squares* indicate prevalence of less than 5%, *green circles* indicate prevalence of 5% to less than 10%, *yellow diamonds* indicate prevalence of 10% to less than 15%, and *red stars* indicate prevalence of 15% or more, (*Reproduced from Journal of Allergy and Clinical Immunology, Odhiambo JA, Williams HC, Clayton TO et al, 124, 1251-8, Copyright 2009 with permission from Elsevier*)

2m

ATOPIC DERMATITIS: TOPICAL TREATMENT OF ATOPIC DERMATITIS

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INTRODUCTION

Topical treatment of Atopic dermatitis (AD) aims at restoring the skin barrier function and inhibit the inflammatory reaction in the skin. It is used in mild to moderate disease, but also as adjuvant therapy in patients needing systemic immunosuppressive therapy. The aim is also to achieve control of the eczema during remission periods, and bring down the number of flares.

KEY MESSAGES

- Moisturizers are basic therapy in atopic dermatitis
- The goal of treatment is to re-establish skin barrier and inhibit inflammation
- Proactive therapy may be the best way to maintain control of the disease

DRUGS

The mainstay therapy of AD is the daily application of moisturizers that upholds the integrity of the skin barrier, and thereby inhibits inflammation. Moisturizers should not be considered as skin care, but as first line therapy for AD. In children with high risk of developing AD, early intervention with moisturizers may decrease the risk of developing AD and later the risk of developing type I allergies. In case of mild to moderate AD the inflammation in the skin must also be treated, and the drug of choice is topical steroids (Figure 1). These should be applied to the areas affected once daily. In small children class I to the face and intertriginous areas and class II to other areas of skin, in older children and adults a class II and class III topical steroid respectively should be used. Topical calcineurin inhibitors (Tacrolimus and Pimecrolimus) can also be used, and generally their efficacy is considered to be as a class II topical steroid. Both can be used in adults and children. New topical drugs for the treatment of AD are emerging with the PDE-4 inhibitors as the first to be licensed, but also the JAK/STAT inhibitors. However, their role in the treatment algorithm of AD remains to be determined.

APPLICATION

Topical drugs should be applied in fingertip units, i.e. the amount of cream with the same diameter as the opening of the tube and the length of the distal phalanx of the finger, covers a skin area of two palms of the hand. During the acute phase of disease, the topical treatment should be applied once per day until the eczema subsides, typically around 2 weeks. If the eczema flares up within very short time of stopping therapy, proactive treatment with application of the topical treatment twice weekly can be considered for both steroids and calcineurin inhibitors. Studies have shown that this strategy results in less use of topical

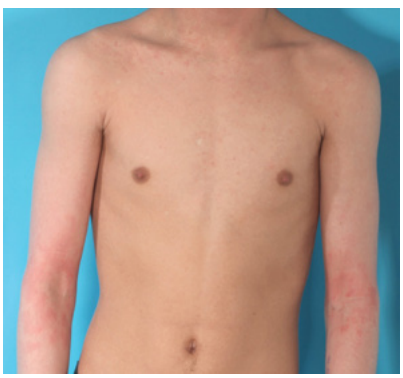

Figure 1 An adolescent boy with mild atopic dermatitis located to the flexural folds on the arms and on the neck

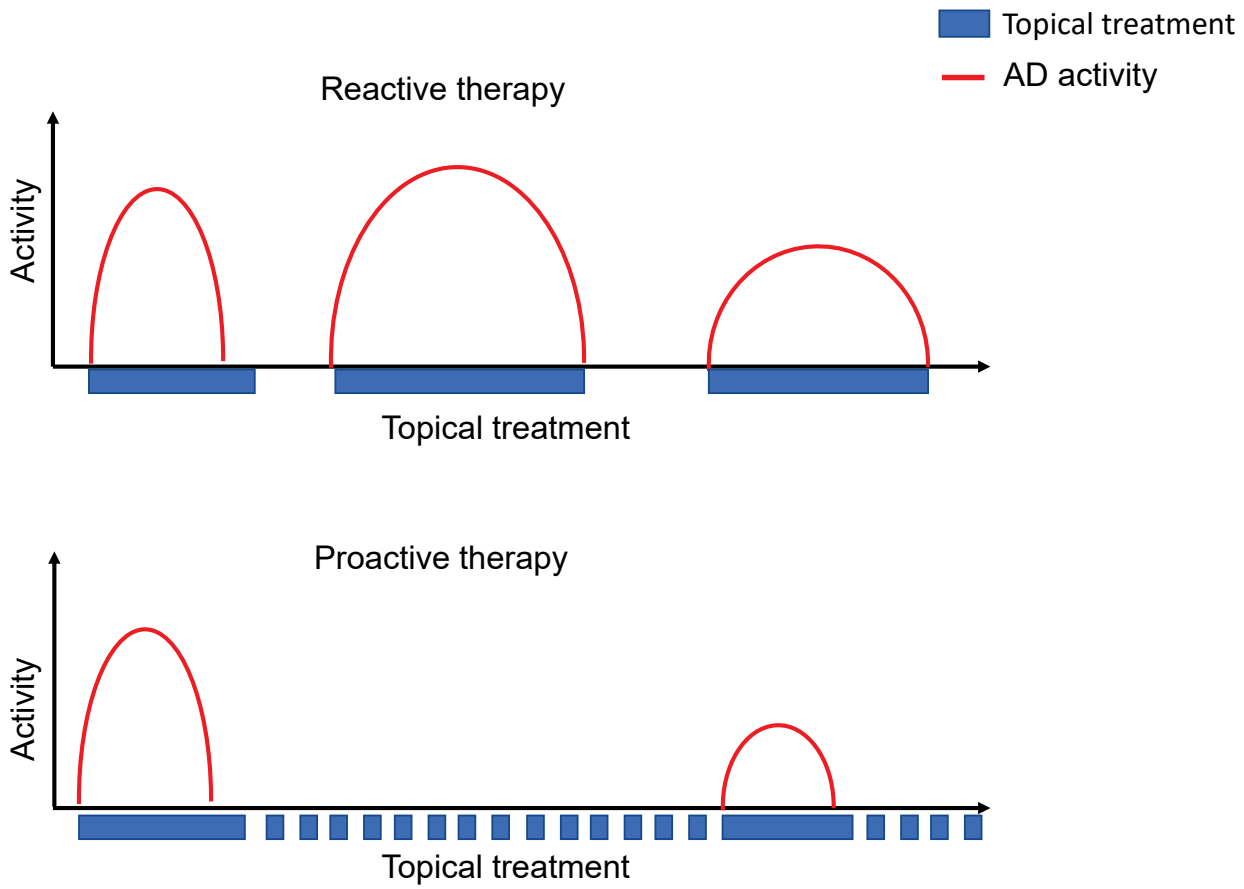

Figure 2 The top panel illustrates the use of reactive therapy. When the eczema flares up (red line) the treatment is instigated (blue blocks) until the eczema subsides. In the lower panel the eczema is treated until it subsides and the topical treatment is continued twice weekly in the areas usually affected by the eczema. At flare up treatment is increased again to once daily until remission, and the twice weekly regime is continued

treatment compared to reactive therapy, and less flares (Figure 2). Most experts agree that systemic treatment should be started if topical treatment exceeds more than 2-300 grams of topical treatment per month without controlling the disease.

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2n

ATOPIC DERMATITIS: SYSTEMIC TREATMENT

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KEY MESSAGES

- Systemic immunos`uppressive treatment has been an option for severe refractory cases for many years although only cyclosporine has been approved for the treatment of atopic dermatitis
- Biologicals (therapeutic antibodies or receptor molecules) targeting the TH2 pathway may be an alternative
- A number of novel target structures have been identified for the treatment of atopic dermatitis and currently many clinical studies are being performed on AD

Most guidelines on the management of atopic dermatitis (AD) recommend systemic treatment when topical treatment alone (i.e. basic therapy, topical corticosteroids, topical calcineurin inhibitors) is not sufficient for the management of the disease (Table 1). Antihistamines have been used for decades to relieve pruritus in patients with AD but only a few randomized controlled trials have been conducted. In the majority they have shown only a weak or no effect in decreasing pruritus or eczema severity. Allergen immunotherapy (AIT) has been studied in a couple of smaller controlled studies. A recent Cochrane review found limited evidence that this approach may be an effective treatment for people with AD. Of note, AIT may well be used in AD when approved indications for this treatment (rhinoconjunctivitis and/or allergic asthma bronchiale) exist in the same patient. Microbial colonization and superinfection may cause disease exacerbations in AD and can justify additional systemic antimicrobial treatment.

Systemic immunosuppressive treatment has been an option for severe refractory cases for many years. Only cyclosporine has been approved for the treatment of atopic dermatitis in adults in most European countries so far. Due to a couple of side effects (e.g. nephrotoxicity, hypertension, photocarcinogenic long term effects) the application of this drug for the indication of AD should be limited to one year if possible. Controlled studies are also available for methotrexate, azathioprine and mycophenolate mofetile for the treatment of AD. Treatments with these drugs have, however, to be performed off label. Importantly, systemic corticosteroids should be used only for short term interventions (i.e. less than three weeks per course) in severe, acute flares of AD.

Biologicals (therapeutic antibodies or receptor molecules) targeting the TH2 pathway may be an alternative. Dupilumab, an anti-IL-4alpha receptor blocking antibody blocking the action of IL-4 and IL-13 has been approved for the treatment of AD in adults in 2017 by the EMEA and the FDA. More recently, this antibody has also been approved for children and adolescent patient older than 12 years and for the treatment of severe allergic asthma bronchiale by these authorities. The benefit/risk ratio of this antibody is good since inflammatory eye diseases and local inflammatory reactions at the injection site have only been described as specific side effects so far.

Unfortunately, none of the mentioned systemic approaches are approved for the treatment of se-

TABLE 1

Available systemic medication for the treatment of AD
A. Anti-inflammatory drugs approved in adults or adolescents in most European countries
Corticosteroids (short term treatment only), Cyclosporine, Dupilumab
B. Anti-inflammatory drugs not approved for AD
Methotrexate, Azathioprine, Mycophenolate mofetile
C. Other approaches of systemic therapies in AD
Histamine 1 receptor blockers (limited effect), AIT (in conjunction with rhinoconjunctivitis and/or allergic asthma bronchiale), antimicrobials in cases of secondary skin infections

TABLE 2

Novel systemic drugs with published data from controlled clinical studies in full papers		
Name of drug	**Target structure**	**Type of study**
A. Antibodies		
Dupilumab	IL-4 receptor, IL-13 receptor	Phase III
Lebrikizumab	IL-13	Phase II
Tralokinumab	IL-13	Phase II
Nemolizumab	IL-31 receptor	Phase II
Fezakinumab	IL-22	Phase II
Tezepelumab	TSLP	Phase II
B. Small molecules		
Baricitinib	JAK 1/JAK 2	Phase II
ZPL3893787	Histamine 4 receptor	Phase II

verely affected children with AD so far.

A number of novel target structures have been identified for the treatment of atopic dermatitis and currently many clinical studies are being performed on AD. Positive outcomes were reported in full papers from phase II studies with anti-IL-13 (lebrikizumab, tralokinumab), anti-IL-31 receptor (nemolizumab), anti-IL-22 (fezakinumab), anti-TSLP (tezepelumab) and on small molecules targeting the histamine-4-receptor (ZPL389) and the JAK1/JAK2 inhibitor baricitinib so far (Table 2).

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20

ATOPIC DERMATITIS: PREVENTION OF ATOPIC DERMATITIS

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KEY MESSAGES

- Prevention of atopic dermatitis has to start early: during pregnancy and/or right after birth
- Most successful targets of primary prevention are improvement of skin barrier function and the gut microbiome

ORIGINS OF ATOPIC DERMATITIS

The highest incidence of atopic dermatitis is observed in the first year of life. However, the prognosis of infantile eczema is good, 65% of children who developed AD in the first year of life will lose their symptoms by age 3, many patients still present at least minor symptoms until adulthood. Atopic dermatitis (or atopic eczema) is related to a Th2 like inflammation, but only 50% show atopic sensitization and approximately 50% of sensitized individuals have clinically relevant food allergy. Only a subgroup with more severe and often persistent disease and early sensitization to aeroallergens may develop allergic airway disease as the "atopic march". In adulthood, atopic dermatitis is much less related to food allergy compared to infancy and early childhood. As causative factors for AD skin barrier impairment has been observed. Approximately 20% of individuals with a more severe type of AD are found to have a filaggrin mutation. Maternal filaggrin mutations increase the risk of atopic dermatitis in children. Interestly, non-atopic individuals with a filaggrin loss of function mutation have a different phenotype: ichthyosis vulgaris, excessive dryness of the skin without inflammation. The skin barrier dysfunction is assumed to facilitate the uptake of allergens via the leaky skin and thus allergic sensitization. Furthermore, inflamed skin is shown to have different microbial colonization, like Staphylococci, being a driving force for inflammation. AD flares seem to be dependent on the skin microbiome. As AD occurs early in life, preventive measures have to be applied immediately after birth or even during pregnancy. Infants with AD were found to have a different microbiome than children without AD or just lower diversity of gut microbiota. In some trials, the difference of the infantile microbiome was also related to birth delivery and number of siblings. Others showed a protective effect of dog keeping, which may be due to increased exposure to commensal bacteria. Keeping a cat seems to increase the risk of AD in young infants with filaggrin mutations. Therefore, interventions influencing the gut microbiome were introduced often, already during pregnancy or directly after birth.

TARGETS FOR PREVENTION IN CONTROLLED TRIALS

As targets for prevention of AD in infancy the following were approached:

- Skin barrier
- Early diet
- Probiotics/synbiotics/gut microbiome

Target skin barrier dysfunction:

There have been randomized controlled trials showing that application of full-body emollient therapy at least once per day starting in the first month of life enhanced skin barrier function and the cumulative incidence of AD at 6 months of age. One of the products which were used in the trials was an ointment containing paraffin, which is known to enhance antimicrobial peptides in the skin. All three products used in the trial (oil, emollient and ointment) achieved a preventive effect.

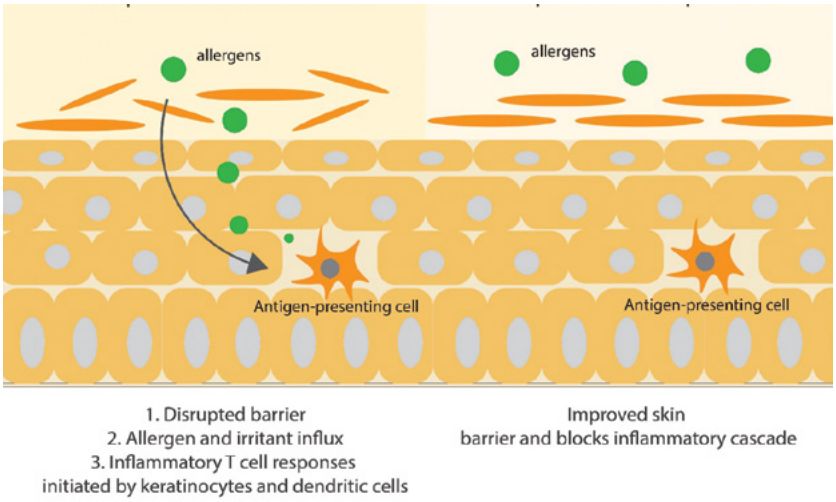

Figure 1 Skin barrier protection might prevent atopic dermatitis development (FLG – Filaggrin)

Hypoallergenic formula in the first 4 months of life

All scientific and clinical societies agree that breastfeeding is the best nutrition for newborns and young infants up to 4-6 months of life. If breastfeeding is not or only partly possible in high risk babies, the GINI trial showed that certain partially and extensively hydrolyzed hypoallergenic formulas are superior to regular formulas in terms of AD prevention. This could not be demonstrated for infants not being at risk for atopy. The problem is that it is not clear which products are AD preventive and if a carry-over effect can be assumed.

Probiotics/synbiotics/microbiome

Probiotic supplementations were performed mainly in high risk families during gestation (mostly during the last trimester) and/or during the first 6 months of life. In a systematic review and meta-analysis mixtures of probiotics, including Lactobacillus, Bifidobacterium and Propionibacterium strains significantly decreased the risk of AD if given pre- and postnatally, while when given prenatally or postnatally only, statistical significance was not achieved. The additional benefit of synbiotic therapy (addition of prebiotics) remains less clear.

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3a

CONTACT DERMATITIS: EPIDEMIOLOGY OF CONTACT DERMATITIS

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KEY MESSAGES

- Contact dermatitis can be divided into irritant and allergic contact dermatitis with irritant contact dermatitis being the most common type
- Contact allergy (sensitisation) is found among 16-28% of adult and 13-23% of children in the general population, while very few studies have evaluated the prevalence of allergic contact dermatitis and no studies the prevalence of irritant contact dermatitis in the general population
- The most common contact allergens are metals, fragrances, preservatives, hair dyes, glues and rubber chemicals

Contact dermatitis can be divided into irritant and allergic contact dermatitis. Irritant contact dermatitis (ICD) is a non-allergic inflammation of the skin to an external agent, most often water and detergents. Allergic contact dermatitis (ACD) is the consequence of exposure to a contact allergen exceeding an individual threshold concentration in a contact sensitised person. Sensitisation (contact allergy) does not always lead to allergic contact dermatitis.

Contact dermatitis is a common disorder, with irritant contact dermatitis being the most common type. However, exact prevalence and incidence estimates in the population are difficult to obtain, as most publications are based on selected patient materials. Furthermore, many studies indicate the number with a positive patch test reaction (contact allergy) and not the prevalence of allergic contact dermatitis. For ICD the figures on prevalence are variable due to differences in the spectrum of irritants, working conditions and protective measures.

TABLE 1

Most common groups of contact allergens
Metals (nickel, chromate, cobalt)
Fragrances
Preservatives
Hair dyes
Glues
Rubber chemicals

A few cross-sectional studies on contact allergy and ACD among adults in the population exist. The Copenhagen Allergy Study from 1990 reported a point prevalence of contact allergy on 15.9% in unselected adults aged 15 to 69. In the TOACS study in 2010 among young adults (29 years of age) the point prevalence of contact allergy was 20.1% and present or past ACD was found in 12.9%. In the TOACS cohort the incidence rate of contact allergy from adolescence to adulthood was 13.4% and 7.8% for ACD. In the Copenhagen Allergy Study 12% of the adult population developed contact allergy during an 8 year follow up period.

The most common contact allergens are metals, fragrances, preservatives, hair dyes, glues and rubber chemicals (Table 1). However, contact dermatitis is a field under constant development because the environment changes over time due to introduction of new chemicals in consumer and industrial products and phasing-out of other chemicals.

Contact allergy and ACD in chil-

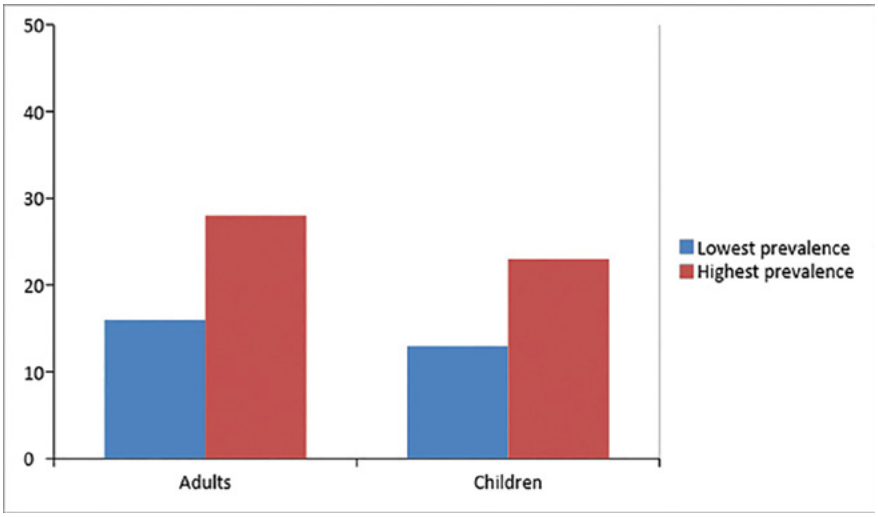

Figure 1 Point prevalence (%) of contact allergy in unselected populations

dren appears to increase, and contact sensitization may already begin in infancy. The most common sensitizers among children are metals, fragrances, preservatives and hair dye. ACD may be difficult to separate from atopic dermatitis in childhood and the diseases may even occur together. Children with atopic dermatitis more often react to components of skincare products.

Adult contact dermatitis is often caused by occupation exposure. Skin diseases constitute up to 30% of all notified occupational diseases and contact dermatitis account for 90-95% of all occupational skin diseases. However, these figures can be biased as national registries are usually incomplete. The average incidence rate of occupational contact dermatitis is around 0.7-1.5 cases per 1.000 full-time workers per year.

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3b CONTACT DERMATITIS: MECHANISMS OF CONTACT DERMATITIS

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KEY MESSAGES

- Allergic contact dermatitis is caused by protein-reactive chemicals
- Contact allergens induce cellular stress responses and activate the innate immune system
- Contact allergens activate pattern recognition receptors such as Toll-like receptors and the NLRP3 inflammasome either directly or indirectly
- Mast cells and neutrophils are crucial innate effector cells in allergic contact dermatitis
- Tissue-resident memory T cells are important effector cells of allergic contact dermatitis
- Interfering with innate immune and stress responses offers new opportunities for therapy

Contact dermatitis is an inflammatory skin disease that is induced by xenobiotic chemicals. The resulting xenoinflammation involves innate immune and stress responses. Irritant contact dermatitis (ICD) is caused by chemical irritants such as detergents and does not involve the adaptive immune system. In contrast, allergic contact dermatitis (ACD) is caused by metal ions and natural or synthetic protein-reactive organic chemicals and is mediated by contact allergen-specific T cells.

The immune response to contact allergens resembles an anti-infectious response. The sensitization phase of ACD is initiated by chemical-induced skin inflammation. Contact allergens activate pattern recognition receptors (PRRs) which normally recognize microbial molecules such as DNA, RNA and cell wall components (Figure 1). Nickel, cobalt and palladium can directly activate the human Toll-like receptor TLR4, the receptor for bacterial lipopolysaccharide (LPS). Experimental contact allergens such as trinitrochlorobenzene (TNCB) or oxazolone indirectly activate TLR2 and TLR4 by induction of hyaluronic acid (HA) breakdown. HA fragments then trigger these TLRs. The production of reactive oxygen species (ROS) is induced by contact allergens. This contributes to the activation of NF-κB and of another PRR, NLRP3 and formation of the NLRP3 inflammasome. This inflammasome then produces mature IL-1β and IL-18 from immature precursors. Contact allergens can activate the inflammasome in an ATP/P2X7R-dependent or –independent manner. These mechanisms must be functional in skin dendritic cells for their activation, migration to skin draining lymph nodes and priming of contact allergen-specific Th1/Tc1 and Th17/Tc17 cells. Other innate immune cells which contribute to the skin inflammation are dermal mast cells and newly recruited neutrophils. Moreover, γδ T cells (DETC in the mouse) contribute for example by IL-17 production.

The elicitation of clinical symptoms requires the recruitment of T cells to the inflamed skin and their production of cytokines and cytotoxic molecules which damage for example keratinocytes. Recent studies have shown the development of tissue-resident memory T cells which are important for recurring ACD and for flare-up reactions.

Tolerance to contact allergens and the immune regulation of ACD in-

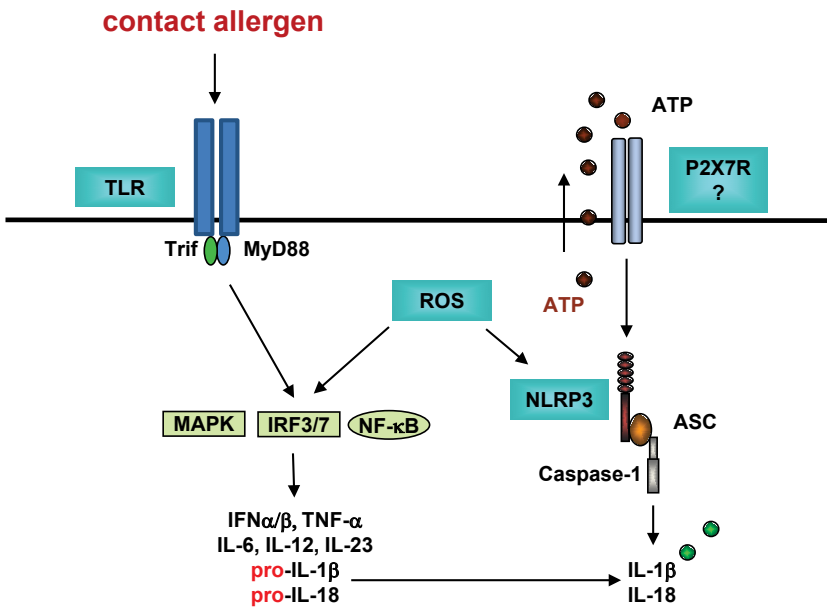

Figure 1 Contact allergens directly or indirectly activate TLRs, ROS production and the NLRP3 inflammasome. P2X7R is involved in inflammasome activation in some cases

TABLE 1

Mechanistic parallels between the mouse CHS model and human ACD		
PRR	**mouse**	**man**
TLR	TLR2, TLR4	hTLR4
contact allergen	**TNCB, DNFB, oxazolone**	**Ni, Co, Pd**
NLR	NLRP3	NLRP3
contact allergen	**TNCB, DNFB, oxazolone**	**Ni, Cr(IV)**

TABLE 2

Potential targets for causative therapeutic strategies in the treatment of ACD *	
target	**treatment**
TLR2, TLR4	TLR antagonists/mAbs
hyaluronic acid fragments (ECM)	**HAdase inhibitors**
ROS	**antioxidants**
P2X7R	**P2X7R antagonists (KN-62)**
NLRP3 inflammasome	inhibitors (glyburide, aspirin etc.)
IL-1β	**IL-1R antagonists/mAbs (Anakinra)**

** Successful experimental approaches for the CHS model are shown in bold blue*

volves IL-10 producing regulatory T cells (Treg) and invariant NKT cells (iNKT).

The parallels between the mechanisms in the mouse contact hypersensitivity (CHS) model and ACD (Table 1), and some T cell mediated adverse drug reactions make the development of drugs that target inflammation as well as the T cell compartment attractive. Several approaches work in the CHS model to prevent sensitization and elicitation (Table 2). Causative treatment of ACD may be possible in the future.

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3c

CONTACT DERMATITIS: CLINICAL FEATURES OF CONTACT DERMATITIS

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KEY MESSAGES

- Acute, subacute or chronic eczema reproducing the area of contact with the culprit allergen is the main manifestation of allergic contact dermatitis
- Hand dermatitis may be a presentation of allergic contact dermatitis, but atopic, irritant and pompholyx may have similar features
- Ectopic, connubial, airborne or photoallergic contact dermatitis may frequently involve the face with eczema or oedema
- Apart from eczema, allergic contact dermatitis may present as erythema multiforme-like, lichenoid, granulomatous, pustular, psoriasiform or lymphomatoid reactions

Contact dermatitis represents a cutaneous reaction to acute or repeated contact with an exogenous chemical. It presents with different clinical aspects depending on the pathomechanisms involved, the allergen/irritant or concomitant aggravating factors (ultraviolet exposure, atopic dermatitis) and the area of skin affected.

CLASSICAL CLINICAL FEATURES OF CONTACT DERMATITIS

The classical presentation of delayed type allergic contact dermatitis (ACD) is an acute eczema (pruriginous erythema with papules, vesicles and possibly exudation) that develops 12-48 hours after contact with the culprit in a sensitized individual. Chronic eczema (erythema with desquamation and lichenification) occurs after repeated exposures. Eczema tends to reproduce the area of contact with the culprit, although it may extend beyond the areas of direct contact (Figure 1 and 2). Exposure to airborne allergens (airborne dermatitis) (Figure 3) or allergens used by our proxy (connubial/by-proxy dermatitis) may have a more peculiar distribution of lesions. In photoallergic contact dermatitis, namely from UV absorbers or topical non-steroidal anti-inflammatory drugs, reactions develop only in areas of simultaneous exposure to the photoallergen and UV light.

HAND AND FACIAL DERMATITIS

In hand dermatitis, where irritant, atopic and allergic mechanisms may concur, apart from vesicles and desquamation, skin dryness, palmar hyperkeratosis and fissures may be the predominant manifestation, as in pulpitis from garlic, *Alstroemeria* or tulip bulbs (Figure 4). Nail dystrophy can follow eczema involving nail folds, as in ACD from (meth)acrylates in artificial nails or long-lasting UV-cured nail varnish. Pompholyx-like eczema (deep vesicles in the lateral aspects of the fingers and palms) can also be a presenting form of ACD or protein contact dermatitis (immediate reactions from contact with proteins, mostly from vegetable or animal products in an occupational setting).

In the face, apart from acute vesicular eczema, oedema involving particularly the eyelids can be the manifestation of contact dermatitis from cosmetics. Particularly in hair dye allergy, the scalp may be spared or have extensive exudation, but the face may be swollen mimicking angioedema or erysipela (Figure 5). Cheilitis, rosacea-like dermatitis, with scattered lesions involving only some areas of the

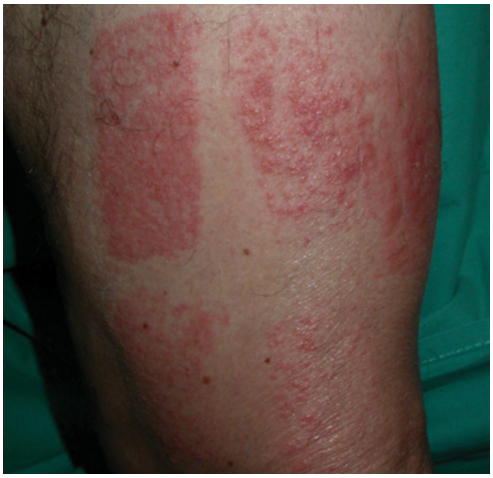

Figure 1 Acute ACD with erythematous and vesicular well demarcated rectangular lesions, coincident of the shape of the transdermal therapeutic system containing rivastigmine

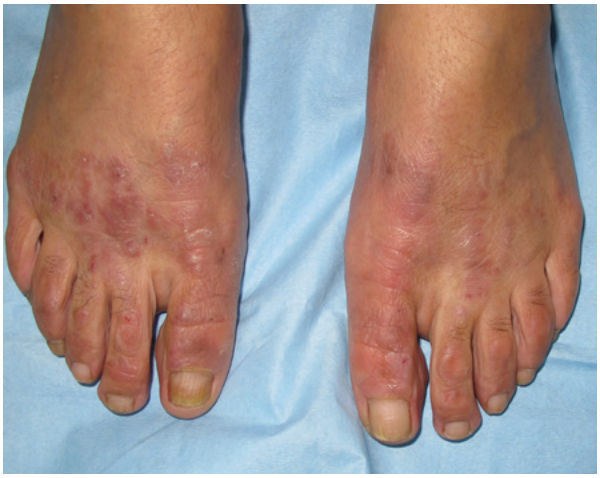

Figure 2 ACD from shoes with a symmetrical localization in the dorsum of the feet, typically sparing the web spaces

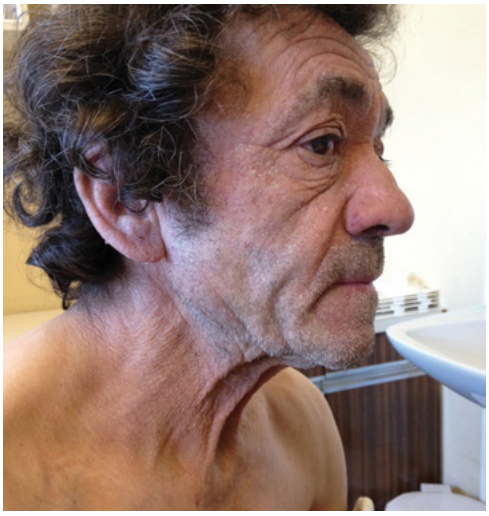

Figure 3 Airborne occupational ACD from isothiazolinones in a painter, affecting only air-exposed areas including those usually spared in photosensitivity (upper eyelids, submandibular area, retroauricular spaces)

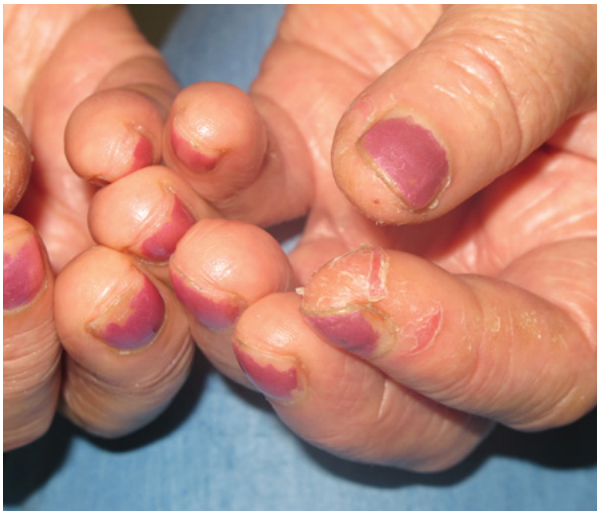

Figure 4 Painful and pruritic pulpitis with fissures due to contact dermatitis from garlic, with positive patch tests to diallyl dissulfide

face, or pigmented dermatitis may be an expression of ACD.

PARTICULAR FEATURES OF CONTACT DERMATITIS

Other clinical features of ACD include: - erythema multiforme-like lesions, specially due to contact with very strong allergens (tropical woods and plants), - lichenoid dermatitis (from metals in contact with mucosae or from photographic colour-developers), - granulomatous dermatitis simulating keloids (from palladium in earrings) (Figure 6a, b), - purpuric dermatitis (ACD from textile dyes or in ACD localized to the legs in patients with chronic venous insufficiency), - pigmented lesions with scarce inflammation (allergy/photoallergy from fragrances), - vitiligo-like lesions (from phenol and cathecol-derived allergens, particularly in patients with darker phototypes), - follicular or pustular and psoriasiform lesions, mostly

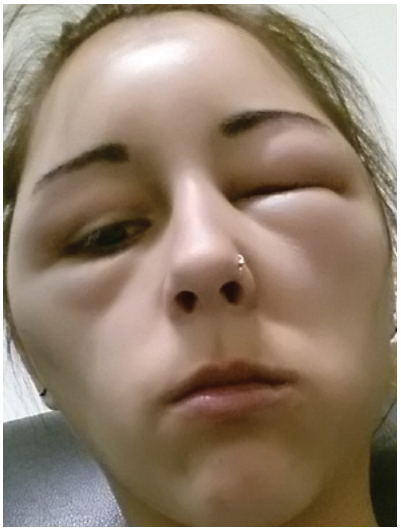

Figure 5 Exuberant oedematous facial reaction that began 24 hours after dying her hair, in a patient sensitized to p-phenylenediamine (PPD) through "Henna" temporary tattoos

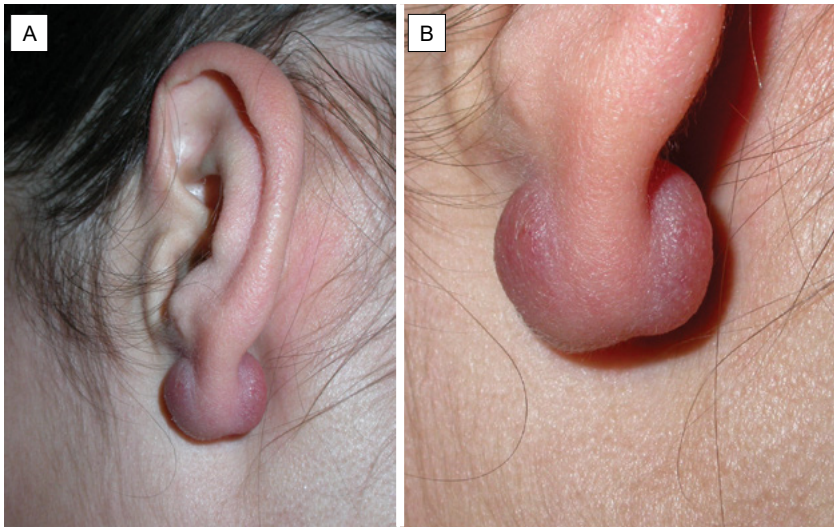

Figure 6 Granulomatous contact dermatitis from earrings (a), that in detail simulates a keloid scar. Patch tests were positive to nickel sulphate and palladium chloride, but Nickel reaction resolved in less than a week, whereas the reaction to palladium was still present at 3 weeks and histology showed a granulomatous reaction

from metals, - lymphomatoid-like lesions, with cutaneous infiltrated plaques and histology simulating a cutaneous T-cell lymphoma, as recently described for methylisothiazolinone.

In individuals previously sensitized through the skin, systemic exposure to the same or a related allergen can induce systemic contact dermatitis presenting as a maculopapular exanthema, with worsening in the buttocks and large body folds (Baboon syndrome), as vesicular hand dermatitis, worsening of dermatitis in previously involved areas or simply as pruritus with no objective lesions.

It is, therefore, necessary to be alert to the distinct clinical features and time course of ACD and perform patch and/or photopatch tests in all suspected cases.

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3d CONTACT DERMATITIS: RESPONSIBLE AGENTS (ALLERGENS AND IRRITANTS) IN CONTACT DERMATITIS

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Contact dermatitis may be of irritant, allergic, or mixed aetiology. Not infrequently, irritant contact dermatitis (ICD) paves the path to allergic contact dermatitis (ACD) by inducing epidermal barrier impairment and inflammatory milieu (Figure 1).

KEY MESSAGES

- Contact dermatitis may be of irritant, allergic, or mixed aetiology
- Haptens are small (MW < 500 Da) and reactive molecules able to penetrate the epidermis and bind to epidermal proteins
- The most important haptens are assembled in a so-called baseline series for routine patch testing, and include metals, fragrances, preservatives, rubber additives and other agents
- Patch testing is indispensable for the diagnosis of contact allergy and has achieved a high level of standardisation

IRRITANT CONTACT DERMATITIS

ICD is typically induced by so-called wetwork, mostly in terms of frequent hand-washing or other contact with water, with or without detergents, or exposure to other irritants, such as organic solvents, acids or alkali, oils, oxidants and reducing agents, and also dry/cold ambient air. ICD may start inconspicuously e.g. as interdigital scaling followed by overt dermatitis, as in trainee hairdressers (Figure 2 and 3). However, ICD can develop at any body site, and also acutely, depending on the irritating exposure. Co-factors such as occlusion or dry-cold weather may facilitate ICD. Work materials have to be marked if "corrosive" or "irritating"; cosmetic and similar products are normally formulated to avoid skin irritation, but susceptible persons may still suffer irritation to these, which needs to be distinguished from contact al-

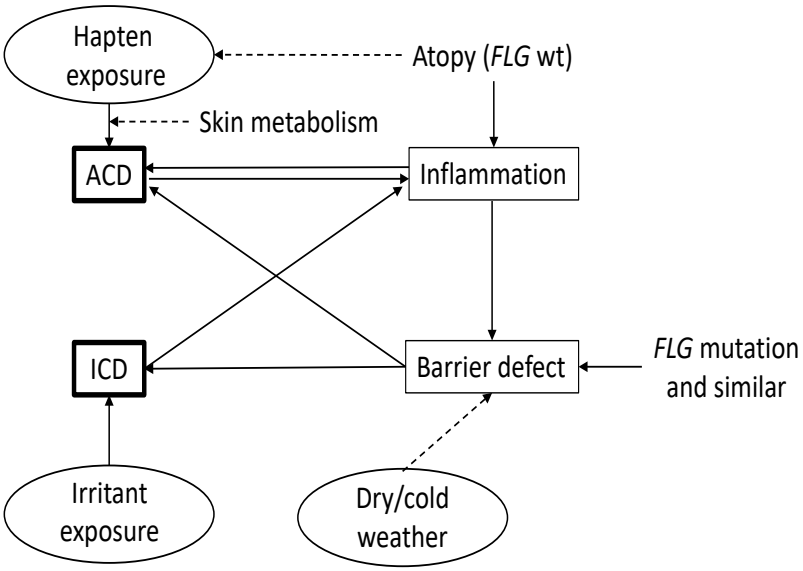

Figure 1 Simple illustration of main associations between exposure (ellipses) and susceptibility factors (no frame), leading to pathological changes (boxes) and ultimately clinical disease (bold boxes). Dashed lines, weak impact; solid lines, important impact

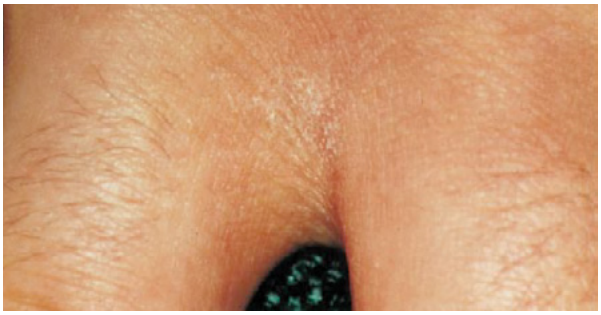

Figure 2 Mild interdigital dermatitis

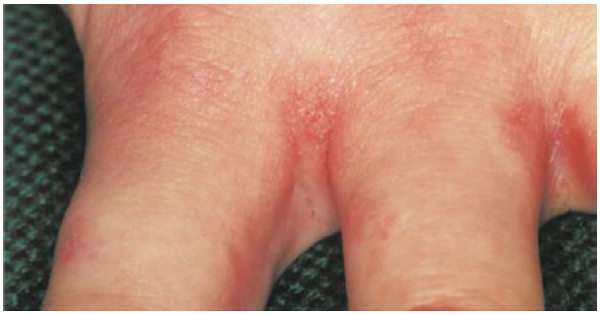

Figure 3 Moderate interdigital dermatitis

lergy to a product ingredient (see below). Standardised skin testing for irritation by a substance or a product is a routine procedure in pre-marketing assessment but has hitherto not been found valuable for clinical routine. Hence, diagnosis and counselling in hand dermatitis patients relies on a standardised history of occupational and non-occupational irritant exposures.

ALLERGIC CONTACT DERMATITIS

The substances inducing contact allergy, and upon subsequent sufficient exposure, eliciting ACD, are usually small (MW < 500 Da) and

TABLE 1

Patch test results with the European baseline series (version until 2018) obtained in general dermatology departments of the ESSCA in almost 30000 patients. Sensitisation prevalence is age- and sex-standardised and accompanied by a 95% confidence interval (CI)

Hapten	Exposures	%pos. (95% CI)
Metals		
Nickel sulfate 5%	Ni-plated or –containing metal objects, incl. jewellery; restricted under REACH in EU	18.1 (17.7-18.6)
Cobalt chloride 1%	Jewellery, leather, cement, hard metal tools, metal cutting, dyes	5.9 (5.6-6.2)
Potassium dichromate 0.5%	Historically (in EU) cement, leather (restricted in EU), chromated objects	3.2 (3-3.4)
Biocides (Preservatives)		
Methylisothiazolinone (MI) 0.2% aq.	Cosmetics (restricted in EU), paints, household and other liquids	7.6 (6.9-8.2)
MCI/MI 0.02% aq.	As for MI	7.3 (6.8-7.9)
MDBGN 0.5%	Banned in cosmetics (EU only), metal working fluids, other liquids	2.2 (1.9-2.5)
Formaldehyde 2% aq.	Technical processes, resins, biocides, incl. formaldehyde releasers	1.7 (1.4-1.9)
Quaternium 15 1%	Cosmetics (formaldehyde releaser)	0.8 (0.7-0.9)
Paraben mix 16%	Cosmetics, topical medications – weak allergen	0.5 (0.4-0.6)
Fragrances		
Fragrance mix (FM) I 8%	Cosmetics, household products, industrial de-/re-odorants	7.3 (7-7.6)
Myroxolon pereirae (balsam of Peru) 25%	Distillates and extracts in cosmetics and historically for topical treatment; fragrance allergy marker	5.3 (5-5.6)
Fragrance mix II 14%	As for FM I	3.8 (3.6-4)
HICC 5%	Main constituent of FM I, banned in EU as of 2020	1.7 (1.5-1.8)
Plastics and rubber		
Thiuram mix 1%	Rubber accelerator, glue	1.9 (1.8-2.1)
Epoxy resin 1%	Diglycidyl ether of bisphenol A, important resin in (boat) construction, sealing, painting	1.1 (1-1.2)

Mercapto mix (MBT, CBS, MBTS, MOR) 2%	As for thiuram mix	0.7 (0.6-0.8)
Mercaptobenzothiazole 2%	As for thiuram mix	0.6 (0.5-0.7)
ptBFR 1%	Glue, especially used in shoes	0.7 (0.6-0.8)
IPPD 0.1%	Black rubber antioxidant	0.6 (0.5-0.7)
Topical medication and cosmetics		
p-Phenylenediamine 1%	(Marker of) main oxidative hair dye substance(s), azo textile dyes	3.2 (3-3.4)
Lanolin alcohol 30%	Emulsifier derived from wool fat; cosmetics and topical medications	1.9 (1.7-2.1)
Neomycin sulfate 20%	Topical aminoglycoside antibiotic, vastly varying use in different countries, eg high in the US	1.2 (1.1-1.4)
Tixocortol-pivalate 0.1%	Marker for topical corticosteroid allergy	0.5 (0.4-0.6)
Budesonide 0.01%	Marker for topical corticosteroid allergy	0.8 (0.6-0.9)
Benzocaine 5%	Topically used anaesthetic; will be replaced by caine mix III also including cinchocaine and tetracaine in 2019.	0.6 (0.5-0.7)
Clioquinol 5%	Historically: topical antiseptic. Deprecated testing in baseline series 2019	0.3 (0.2-0.4)
Plant constituents		
Colophonium 20%	Mixture of resin acids from Pinus spp., used as tackifier, glue, tall oil in cutting fluids, paper/cardboard etc.	2.8 (2.6-3)
Sesquiterpenlactone mix 0.1%	Mix of 3 important allergens in Compositae plants	0.7 (0.6-0.9)
Primin 0.01%	Historically: main allergen of Primula obconica. Deprecated testing in baseline series 2019, because primin-free cultivars prevail	0.2 (0.2-0.3)

All allergens in petrolatum (pet.), except where indicated otherwise: aq.: water; MCI, methylchloroisothiazolinone; MI, methylisothiazolinone; MDBGN, methyldibromo glutaronitrile; ptBFR, p-tert-butylphenol formaldehyde resin; IPPD, N-isopropyl-N'-phenyl-p-phenylenediamine; HICC, hydroxyisohexyl 3-cyclohexene carboxaldehyde.

reactive haptens, thereby capable of (i) penetrating the epidermis and (ii) binding to epidermal proteins, both prerequisites for the development of contact allergy. Thousands of man-made or natural substances or mixtures (eg extracts) have been described as haptens causing ACD. The clinical picture is highly variable, depending on (i) hapten and (ii) type of product or other contact. While acute ACD can sometimes be traced to a certain exposure or even hapten, combining history and clinical picture, this is more difficult in chronic ACD. The standard procedure for the diagnosis of contact allergy is patch testing, which has, in the meantime, achieved a high level of standardisation. However, correct interpretation does require considerable experience. The most important haptens used in routine patch testing are assembled in a so-called baseline series, and include metals, fragrances, preservatives, rubber additives and other agents; table 1 illustrates this scope based on results obtained 2013/14 by the European Surveillance System on Contact Allergies. A broader overview on the current spectrum of new allergens and well-known allergens encountered in new exposure contexts has been reviewed recently.

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3e

CONTACT DERMATITIS: DIAGNOSIS OF CONTACT DERMATITIS

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KEY MESSAGES

- The choice of diagnostic tests depends on the subtype of contact dermatitis
- No diagnostic tests exist for irritant and phototoxic contact dermatitis
- An exposure analysis and identification of the potential offending agent in the environment is crucial for being able to make the diagnosis of contact dermatitis

DEFINITION AND TYPES

Contact dermatitis is defined as an inflammatory skin disease caused by exposures to harmful agents in the environment. These agents can be allergens (proteins or chemicals) or irritants. In rare cases these need UV light to become either photo-allergens or photo-irritants. Typical examples of photo-allergens are chemical sunscreens, while typical examples of photo-irritants are furocoumarins in plants such as hogweed, lime or parsnips.

The different main types of contact dermatitis are given in Table 1.

CHARACTERISTICS

Contact dermatitis is characterised by an unsharp demarcation between involved and uninvolved skin and different types of elements present at the same time, such as erythema, papules and vesicles. Contact dermatitis will appear at the skin sites primarily in contact with the agents, e.g. allergic contact dermatitis to a fragrance ingredient in a deodorant will start in the axilla, where it is applied. Allergic contact dermatitis may spread, if exposure continues and will over time become scaly.

Airborne contact dermatitis will appear at skin sites not covered by clothes typically at the neck, face and hands. Systemic contact dermatitis is a rare form of contact dermatitis and a special entity, where a person previously sensitized to a hapten by skin contact, reacts at systemic exposure usually by ingestion. The clinical presentation may vary from a vesicular hand eczema, flexural dermatitis to general rash.

DIAGNOSIS

The diagnosis of contact dermatitis requires typical clinical symptoms according to the subtype of contact dermatitis (Table 1); a positive diagnostic test, if available (Table 1); current exposure either to the allergen, which has given a positive test and /or current exposure to a skin irritant in a sufficient amount; the exposure should be of a nature and magnitude so that it partly or fully explains the dermatitis; and a time relationship between exposure to the agent in question and development/ worsening of contact dermatitis is present.

The two most frequent types of contact dermatitis are allergic and irritant contact dermatitis. To make the diagnosis an exposure analysis is needed, where exposure to the allergen(s)/irritants in question is identified and if possible quantified. For some allergens spot tests exist which can identify the allergen in the environment e.g. for nickel and formaldehyde. In many cases allergens are identified by scrutiny of ingredient labels of products or safety data sheets. Exposure to foods and wet work, and glove use are described and

TABLE 1

Types of contact dermatitis and main diagnostic tests

Type	Main symptoms	Agent	Test
Allergic contact dermatitis	Dermatitis on contact site. Often spread.	Sensitizing chemicals (haptens)	Patch test
Irritant contact dermatitis	Dermatitis on contact site. Rarely spread.	Skin irritants eg. detergents	None
Protein contact dermatitis	Urticaria, may develop into dermatitis if exposure continues	Proteins eg. food	Prick-prick with suspected agents typically food
Photoallergic contact dermatitis	Dermatitis on contact sites mainly on light exposed areas.	Chemicals turning into haptens by UV exposure	Photopatch test
Phototoxic contact dermatitis	Sharp limits. Looks like a sunburn, may be streaky (if by plants) and bullous. Appears on sun-exposed areas.	Chemicals inducing cell-damage and inflammation at UV exposure	None
Airborne contact dermatitis	Dermatitis at skin sites not covered by clothes, eg. neck, face, dorsum of hands.	Sensitizing chemicals, which are airborne	Patch test
Systemic contact dermatitis	Several different presentations.	Sensitizing chemicals absorbed e.g. through the GI system	Patch test Blinded peroral provocation

quantified. It is well established that wet work of 2 hours or more qualifies, in cases the other criteria are fulfilled, for the diagnosis of irritant contact dermatitis.

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3f

CONTACT DERMATITIS: TREATMENT AND PREVENTION OF CONTACT DERMATITIS

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KEY MESSAGES

- Specific diagnosis includes identification of irritant or relevant allergen exposures, as avoidance of irritant and/or contact allergens is essential in both prevention and treatment of contact dermatitis
- Patient education leading to self-management is beneficial for risk patients, i.e. those with atopic tendency or in wet work occupations
- Optimal skin barrier function through use of moisturisers is important in successfully managing contact dermatitis
- The choice of medical treatment depends on severity, duration and site of the eczema

Contact dermatitis (CD) is influenced by genetic as well as environmental factors (Table 1). Irritants and allergens penetrate the epidermis, and an intact skin barrier is of pivotal importance in the prevention and management of CD. The optimal management of CD involves accurate diagnostics, allowing for avoidance of relevant irritant or allergen exposure, restoration of the skin barrier function, resolution of inflammation and prevention (Figure 1).

DIAGNOSIS AND TESTING

Irritant CD (ICD) is more common than allergic CD (ACD) and constitutes around 3/4 of all cases of CD. Differentiation between ICD and ACD is important, since no healing of CD should be expected if a relevant contact allergy is overlooked. The art of patch testing includes planning of the test, reading the reactions, and determining the relevance of positive reactions, all three steps requiring experience. If positive patch tests are found to allergens to which there is a current exposure, the eczema may be interpreted as ACD, and avoidance of the specific allergen(s) is decisive for healing. The diagnosis of ICD is based on a relevant irritant exposure, (i.e. wet work, food, oils or other irritants) as well as excluding relevant contact allergies, and in this situation minimizing harmful irritant exposures is crucial.

AVOIDANCE AND SELF-CARE

With respect to prevention of ICD dose-response is important, and patients should be educated to minimize irritant exposures (Figure 2). With respect to prevention of ACD sensitization may be prevented by regulation/legislation regarding allergen exposure, at work as well as in private life. Knowledge about prevention is essential for self-care, and patient education given ei-

TABLE 1

Endogenous and exogenous factors may contribute to development of irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD)

	Endogenous factors	Exogenous factors
ICD	**Atopic dermatitis** • Filaggrin deficiency • Impaired barrier function	**Exposure to irritants** • Cold weather • Low humidity
ACD	?	**Exposure to allergens**, depending on • Concentration • Occlusion • Size of exposed area

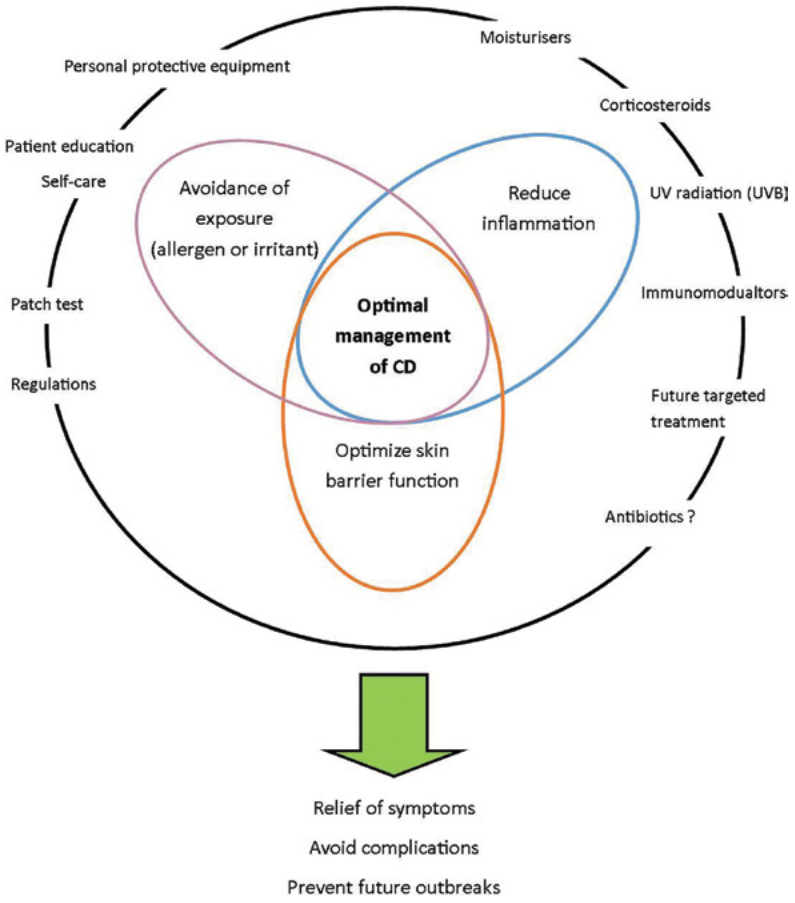

Figure 1 Optimal management of contact dermatitis (CD). The three different aspects to achieve optimal management of CD and the instruments used

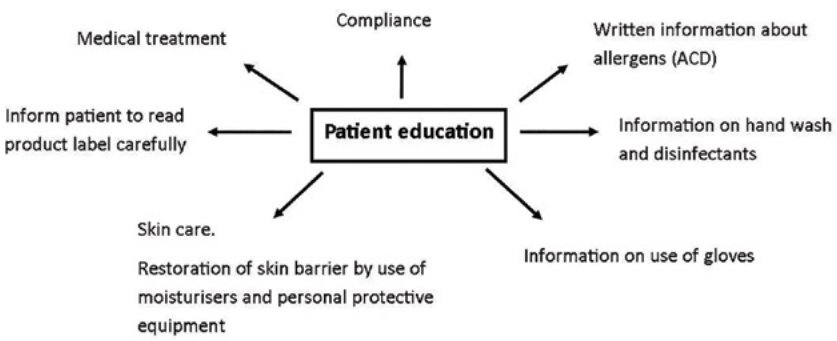

Figure 2 Patient education of contact dermatitis involves several aspects

ther to the individual patient or in groups is highly important.

MEDICAL TREATMENT

Although avoidance of irritants and allergens should lead to healing of eczema, this is unfortunately not always the case.

Moisturisers are essential to maintain and restore optimal skin barrier function. Topical corticosteroids are used as first line treatment, applied once daily for a shorter period of time until the eczema has healed, and thereafter as proactive treatment with application twice weekly for some time. Whereas the effectiveness of corticosteroid treatment is well-documented in ACD, the effects on ICD are more ambiguous, and here restoration of the barrier is of outermost importance.

UV light (UVB or alternatively PUVA) is effective, however also time consuming for the patients. Regarding systemic treatment only alitretinoin is licensed for treatment of hand eczema, however azathioprine, methotrexate, ciclosporin and other immunosuppressants are also used. Systemic treatment is restricted to severe, refractory cases of CD. Medications targeting exact mediators or pathways of inflammation are emerging.

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3g

CONTACT DERMATITIS: ALLERGIC CONTACT DERMATITIS

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KEY MESSAGES

- Allergic contact dermatitis is common and may be diagnosed by patch testing and exposure analysis indicating relevant exposure
- Irritant contact dermatitis is a differential diagnosis which is diagnosed by exposure analysis and knowledge about irritants
- Atopic dermatitis increase the risk of other eczemas and represent a differential and competing diagnosis

Acute allergic contact dermatitis (ACD) is characterised clinically by rapid development of erythema and edema, which often leads to vesicle and even bulla formation (Figure 1). During chronic exposure to a contact allergen, ACD will also be characterised by xerosis and scales, and sometimes even hyperkeratosis and fissures.

ACD is an acquired immune response where circulating memory T cells (upon recognition of the allergen) will settle in the skin where the allergen exposure happens, and sometimes even to skin sites with historical ACD reactions. Since many contact allergens can also irritate the skin, a mixture of ACD and irritant contact dermatitis (ICD) is often observed. Skin barrier impairment will facilitate allergen penetration, and ICD may therefore tend to precede ACD.

There is no good way to clinically discriminate between ACD and ICD when located on the hands, apart from subtle clinical signs, e.g. ICD often begins with dermatitis located interdigitally and is initially dominated by xerosis and scales, whereas ACD typically begins with vesicles and on skin sites, e.g. the fingertips, where the individual has direct and prolonged skin contact to a source of an allergen (Figure 2). ICD is mostly restricted to the face, hands and feet, whereas ACD can occur on all body sites.

Atopic dermatitis (AD), a chronic disorder normally located to the flexure sites in older children and adults, is usually straightforward to distinguish from ACD. AD rarely shows vesicles, but ACD overlying AD may be difficult to recognize clinically. Similar, systemic allergic contact dermatitis which occurs when a contact allergic individual is systemically exposed to a contact allergen, has a predilection for the flexural skin areas and may therefore mimic AD. If there is suspicion of ACD, an exposure analysis is mandatory along with a medical history indicating time from exposure to onset of symptoms and ACD. Then, patch testing can be performed including relevant and possible contact allergens that may have elicited the disease.

Since ACD is a delayed type hypersensitivity reaction, there is normally a crescendo pattern in the patch test readings, where positive and allergic skin reactions gradually become stronger over the 1-week schedule. In contrast, irritant skin reactions during the patch test will show a decrescendo pattern, i.e. reactions become weaker during the first week of testing. Common allergens include metals, fragrances, preservatives, hair dyes, glues and rubber chemicals. A patient with ACD should be free of dermatitis, 1-9 months after complete avoidance of the allergen.

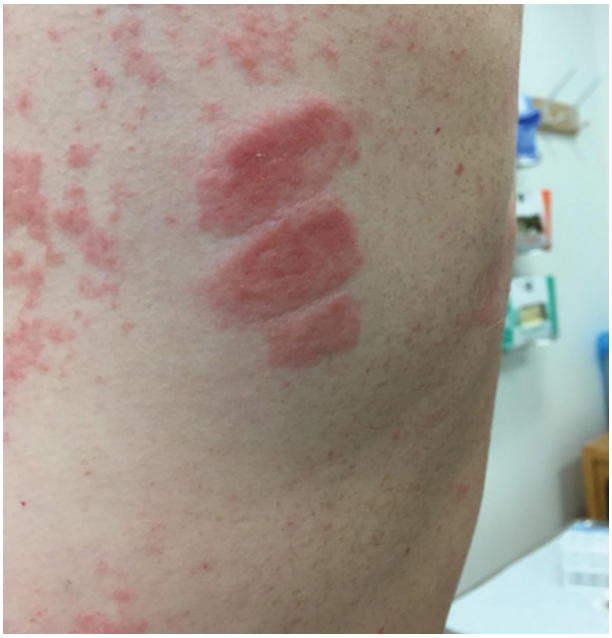

Figure 1 Acute allergic contact dermatitis to poison ivy. Three digits from the patients has been placed on the trunk

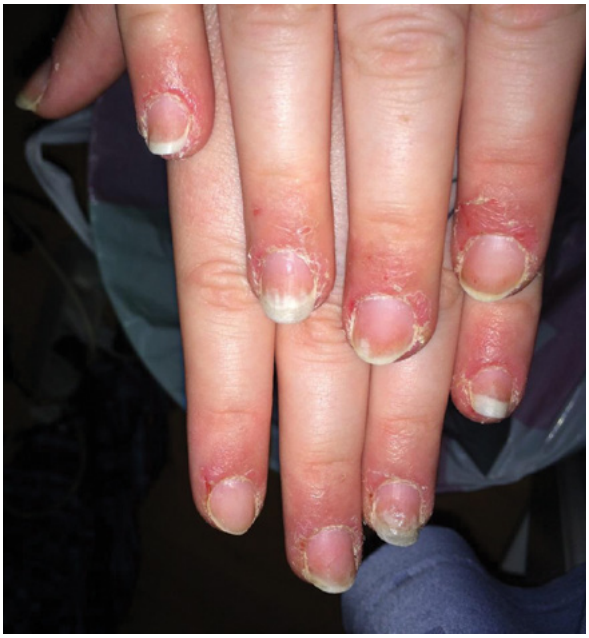

Figure 2 Chronic allergic contact dermatitis from acrylate exposure in artificial nails

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3h

CONTACT DERMATITIS: IRRITANT CONTACT DERMATITIS

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CONTEXT

Irritant contact dermatitis (ICD) is an eczematous reaction caused by an irritant exposure. The pathogenesis is multifactorial and complex, related to both individual and environmental factors. The prevalence of ICD outnumbers by far allergic contact dermatitis. The localization of ICD is mainly on the hands due to the repeated exposure of irritants to this specific part of the body.

KEY MESSAGES

- Irritant contact dermatitis (ICD) accounts for 70-80% of all cases of contact dermatitis
- Different subtypes of ICD include an acute and a chronic form
- Diagnosis of ICD is based on exposure assessment and exclusion of relevant contact allergies. Clinically, the distinction from allergic contact dermatitis is not possible, and all cases of contact dermatitis should undergo patch testing
- Restoration of the skin barrier function is essential in the treatment of ICD. Cornerstones of treatment include counseling with focus on irritant avoidance and use of moisturizer

MECHANISMS

ICD is a heterogeneous disease, caused by an irritant physical or chemical exposure, which damages the epidermis by direct cytotoxic effect without preceding sensitization. Though not fully clarified, the injury of the skin triggers an inflammatory cutaneous response by the innate immune system through compromising keratinocytes and subsequently hyperproduction of proinflammatory cytokines and chemokines, inducing inflammation (Figure 1). The chemical substance, concentration and area of exposed skin are factors of importance for the development of ICD. Furthermore, individual factors, particularly a history of atopic dermatitis, may concomitantly be present and involved in the pathogenesis of the ICD, as the atopic dermatitis contributes to decreased skin barrier function, particularly for individuals with filaggrin mutations. Different irritants induce clinically different reactions, and the response to one irritant in an individual does not necessarily predict the response to other irritants. Increased skin susceptibility and reactivity has led to the concept "sensitive skin", as some subjects develop ICD while others do not, when exposed to the same exogenous conditions. Finally, ICD is associated to the female gender, probably due to a higher degree of irritant exposure.

CLINICAL PRESENTATION

The broad clinical spectrum of ICD includes an acute and a chronic form. The eczema is limited to areas in contact with the irritant, which contrasts with the allergic contact dermatitis (Figure 2). The characteristics of the acute ICD include erythema, infiltration, and more rarely vesiculation. Dryness, fissuring, and hyperkeratosis characterize the chronic ICD.

The diagnosis is based on the clinical presentation of eczema in combination with a documented relevant irritant exposure, exclusion of relevant contact allergies, and exclusion of other potential diagnoses (Table 1).

MANAGEMENT

Avoidance of irritant exposures is essential both at home and at

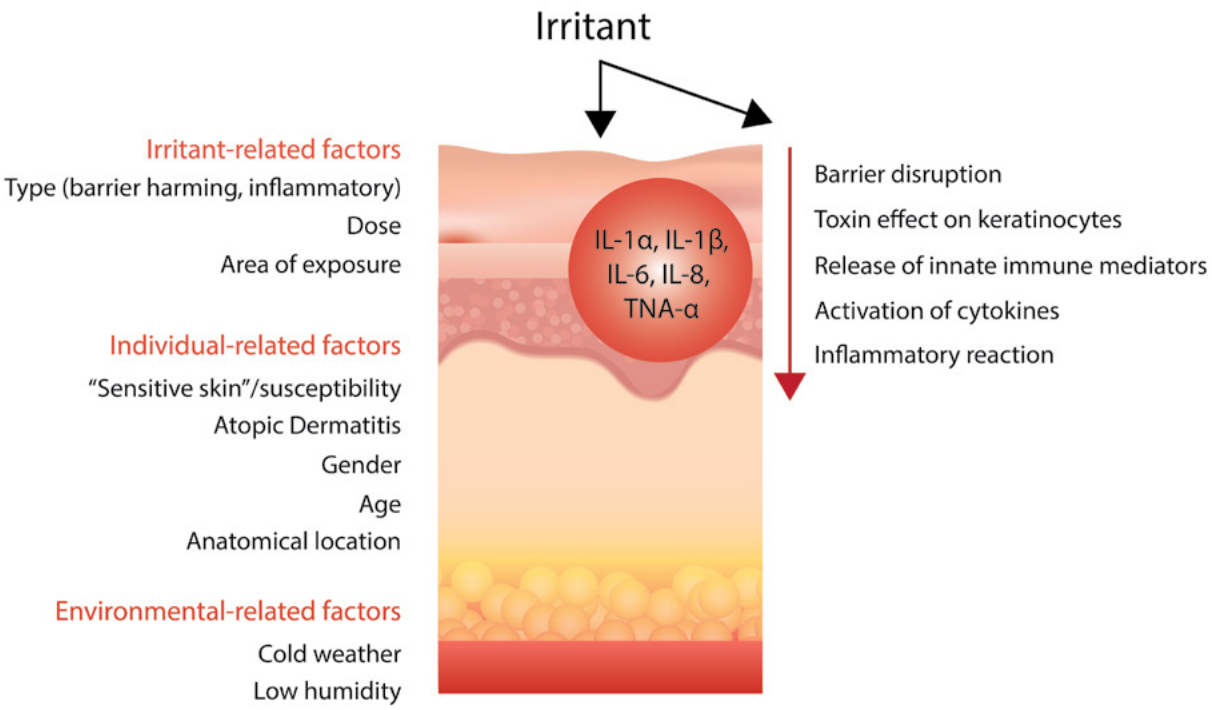

Figure 1 Immune mechanism in the pathogenesis of irritant contact dermatitis (ICD). An irritant damages the epidermis by direct cytotoxic effect of the keratinocytes. Thereby, cytokines are activated by the innate immune system, resulting in an inflammatory skin reaction. Irritant-, individual-, and environmental-related factors for the skin barrier function and development of ICD are illustrated

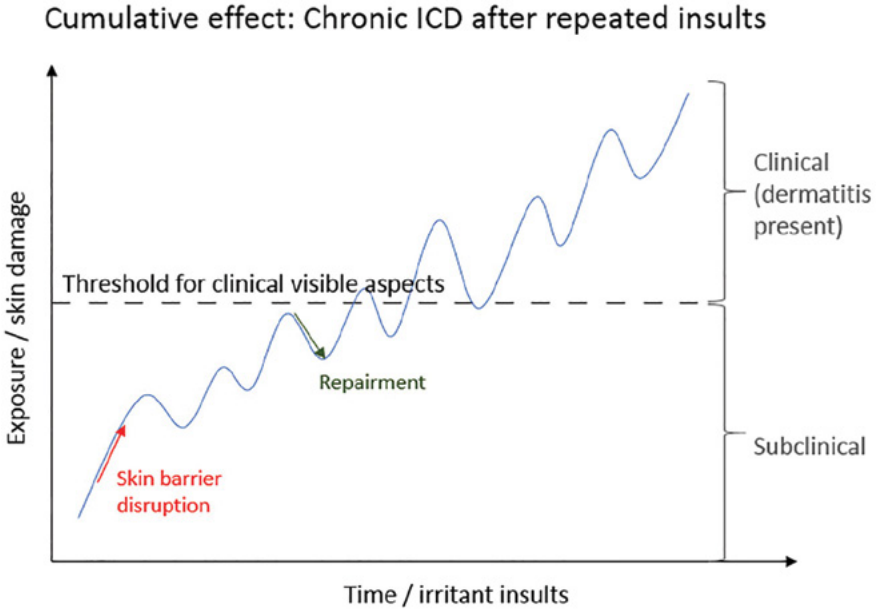

Figure 2 The cumulative, chronic irritant contact dermatitis (ICD) as a function of repeated irritant insults. Irritant exposure damages the skin barrier. After repeated irritant exposures the skin barrier disruption becomes clinically present as eczema

TABLE 1

Comparison of irritant contact dermatitis versus allergic contact dermatitis

	Irritant Contact Dermatitis (ICD)	Allergic Contact Dermatitis (ACD)
Location	Limited to sites of exposure	Often disseminates
Mechanism	Cytotoxic reaction	Type IV reaction
Immune response	Innate immunity	Innate and adaptive immunity
Elicited by	Irritants	Allergens (small molecules)
Personal risk factors	Atopy	-
Environmental risk factors	Exposure	Exposure (duration, concentration, occlusion)
Percentage of all contact dermatitis cases	70-80 %	20-30 %
Diagnosis	Patch test should be performed to exclude relevant contact allergies	Patch test should be performed and in case of positive reactions the relevance of these should be concluded
Treatment and prevention	Identification and avoidance of irritant Moisturizers Counselling regarding irritant avoidance	Identification and avoidance of allergen Moisturizers Topical and systemic steroids Counselling regarding allergen avoidance
Prognosis	Acute: disappears within days to weeks after removal of irritant Chronic: often persists after irritant removal	Often persists after allergen removal

the workplace, either by change of work tasks or by use of personal protective equipment, barrier creams, disinfection instead of hand washing, and glove usage when doing wet work tasks. Moisturizer helps restoring the skin barrier function and is advised, and UV radiation can be beneficial. Treatment of severe, refractory ICD located on the hands may include alitretinoin or immune suppressive therapy.

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3i

CONTACT DERMATITIS: PROTEIN CONTACT DERMATITIS

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INTRODUCTION

Hjorth and Roed-Petersen defined protein Contact Dermatitis (PCD) in 1976. It is an immediate eczematous dermatitis induced after contact with proteins. Thirty-three food caterers suffering exacerbation of the itch, followed by erythema and vesicles immediately after contact with meat, fish and vegetables were described. Application of the relevant foods to the affected skin resulted in either urticaria or eczema. Atopy and PCD are associated in approximately 50% of affected patients. PCD was described in parallel with the Contact Urticaria Syndrome (CUS). This environmental induced syndrome shows heterogeneous clinical manifestations, from contact-induced wheals (Contact Urticaria – CoU) to contact induced eczema (PCD) and include local and systemic manifestations with a common denominator, its immediate appearance after exposure to the triggering agents. The occupational burden due to PCD and CoU is relevant. PCD usually involve food caterers, sellers or handlers.

CLINICAL AND ETIOLOGICAL DIAGNOSIS

PCD is considered a special type of eczema based in the nature of the trigger and the immunological pathway involved. Proteins (molecular weight 10,000 to several hundred thousands) can induce immunological CoU and also PCD and be responsible of chronic and recurrent eczema. Fingertip dermatitis, hand, wrists and arms are the more frequently body sites involved. Some cases of chronic paronychia were considered a variety of PCD, with redness and swelling of the proximal nail fold e.g. after handling food or natural rubber latex (Figure 1). An urticarial or vesicular exacerbation can be noted few minutes after the contact of the causal agent, especially on previously affected skin. As for CoU extra-cutaneous symptoms can appear when PCD is present, as rhinoconjunctivitis or asthma and even anaphylaxis. An "Oral Allergy Syndrome" with abdominal pain, diarrhoea may occasionally

KEY MESSAGES

- Protein contact dermatitis (PCD) shows an important burden that includes an impairment in the patient quality of life and a social impact based on its occupational relevance and health resources expenses
- An early and correct clinical suspicion and the study of each suspected case based on an accurate diagnostic protocol is still an unmet need
- Physicians should be capable to recognize clinically typical signs and symptoms of PCD
- An early diagnosis decreases the burden of the disease for the patient

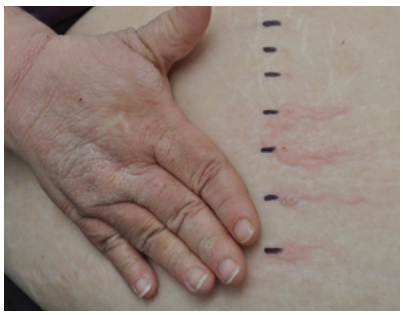

Figure 1 Chronic eczema at the dorsum of the hands and chronic paronychia due to contact with different fishes, working as fish seller

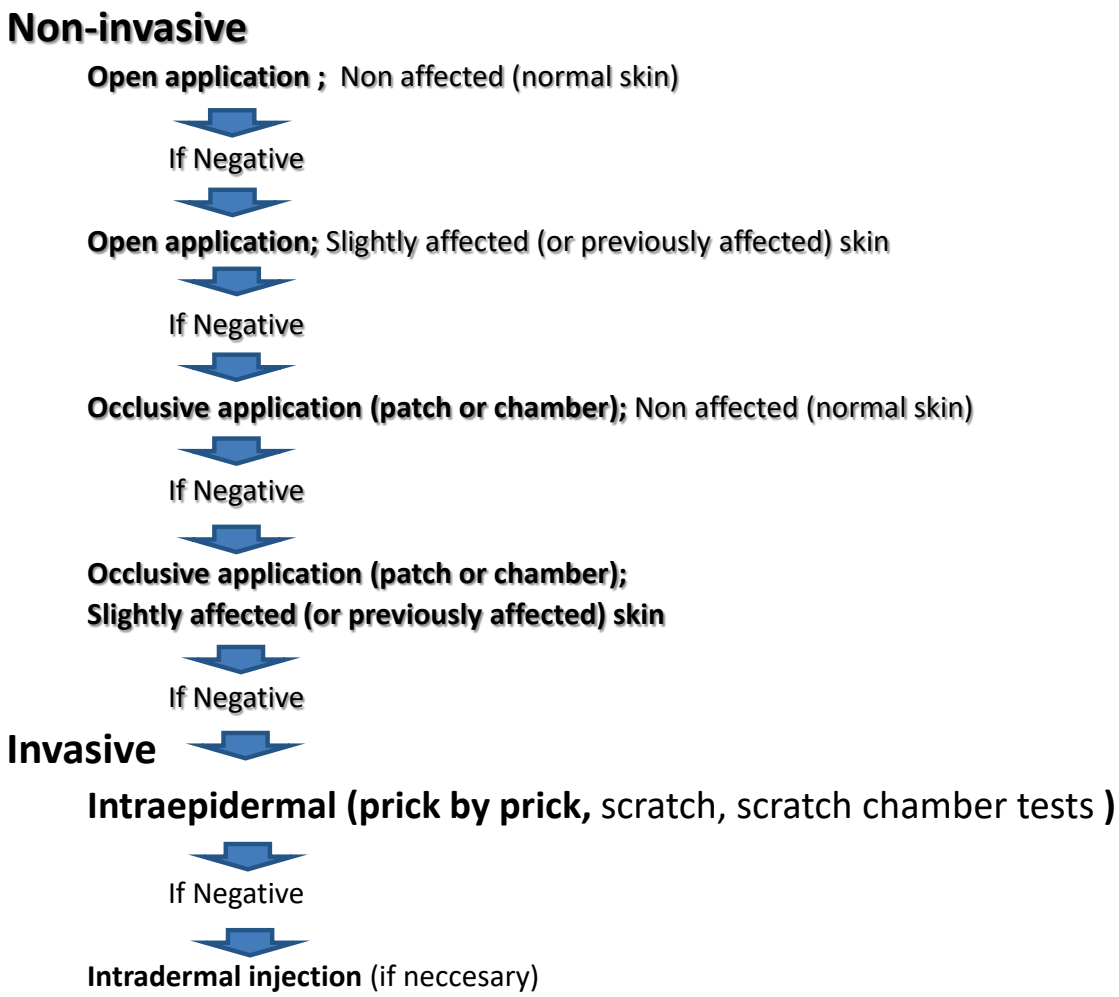

Figure 2 Algorithm of cutaneous provocation test to assess protein contact dermatitis

develop when the allergen comes in contact with the oropharyngeal mucosa . PCD belongs to the first staging of the CUS as CoU does. The same protein can be responsible of both clinical entities in the same patients showing eczema and wheals. Both immediate reactions can be maintained chronic by an accumulative exposure to the contact allergen.

Diagnosis of immediate skin contact reactions as PCD is based on full medical history and skin testing with suspected substances (Figure 2, 3).

PATHOGENESIS

A combination of types I and type IV allergic skin reactions, the latter supported by positive delayed patch tests, has been suggested as PCD pathogenesis. PCD is an eczematous IgE-mediated reaction through proteins in which cutaneous barrier perturbation due occupational tasks facilitates sensitization.

MANAGEMENT AND TREATMENT

PCD clinical symptoms are determined by the route, duration and extent of exposure, the inherent sensitizing properties of the allergen, and an individual's genetic and/or acquired susceptibility. Although topical and systemic immunomodulatory treatments (corticosteroids or calcineurin inhibitors) restore normal skin homeostasis, discovering the responsible agent is required to identify the correct avoidance of the eliciting trigger.

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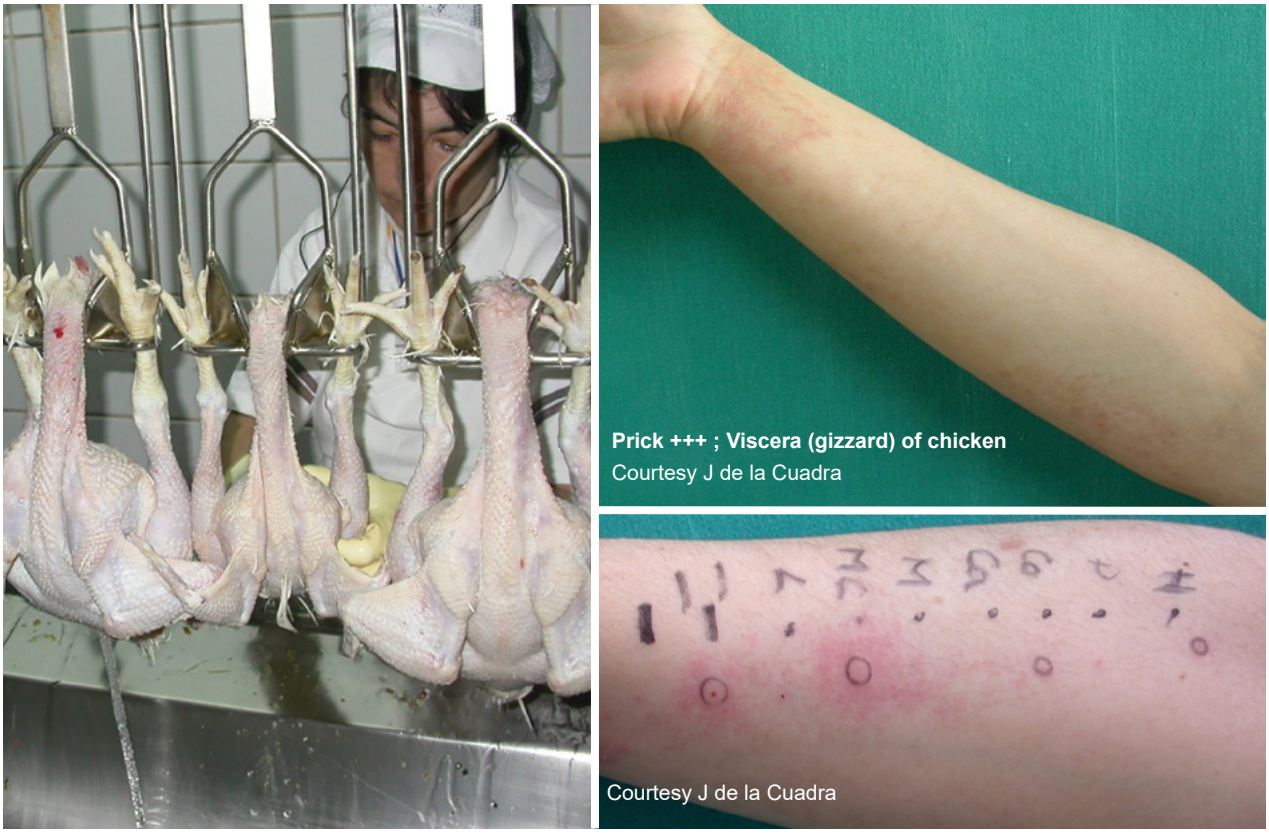

Figure 3 Occupational PCD in the wrist induced by the chicken viscera (gizzard) showing a positive Prick by prick. (*By courtesy Dr Jesus de la Cuadra. Valencia. Spain*)

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CONTACT DERMATITIS: AIRBORNE CONTACT DERMATITIS

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KEY MESSAGES

- Airborne contact dermatitis affect skin areas exposed directly to the environment
- The most susceptible skin area is the upper eyelids
- Airborne contact dermatitis is often occupationally related
- Airborne contact dermatitis may be overlooked because atopic dermatitis, seborrheic dermatitis and photodermatitis may have similar clinical presentation
- Common allergens include *Compositae* plants, uncured resins from sanding of surfaces, and preservatives from water-based paints

The clinical presentation of airborne contact dermatitis is characterised by erythematous, scaly itchy dermatitis on the face and neck, and other skin areas exposed directly to the environment: hands, wrists, and forearms. Covered areas such as lower legs may also be involved due to airborne materials trapped under trousers. The most susceptible area for airborne contact dermatitis is the upper eyelids where it often starts due to the thin skin.

The diagnosis of airborne contact dermatitis may easily be overlooked because other common dermatoses, such as atopic dermatitis, seborrheic dermatitis and photodermatitis may have a similar presentation. Many cases are discovered because they are occupationally related, and the patients themselves get the suspicion.

Both irritants and allergens may be the culprits. Among the common irritants are fiberglass and wood dust. Airborne contact allergens may appear as volatile compounds, as fragrance terpenes or as dust particles carrying the allergen. Among the most common occupationally related contact allergens causing airborne contact dermatitis are epoxy compounds and acrylates (as reported for example from the windmill industry). Uncured resin may be airborne during sanding of product surfaces.

Non-occupational allergic airborne contact dermatitis may be caused or elicited from budesonide-containing aerosols in relation to treating rhinitis and asthma patients. Further, other common sources include the preservative methylisothiazolinone in water-based paint. Methylisothiazolinone (MI) may be released over weeks from newly painted rooms and cause facial allergic contact dermatitis in individuals previously sensitized to methylisothiazolinone from cosmetics.

An important cause of airborne allergic contact dermatitis is Compositae plants (*Asteraceae*). It may develop as an occupational disease among gardeners but is more common as a non-occupational cause in middle-aged individuals with multiple contact allergies. It often starts as hand dermatitis, later spreading to the face with typical exacerbation in spring and early summer.

It may be persistent in severe cases and mimic chronic actinic dermatitis. The Compositae allergens are sesquiterpene lactones present in living as well as dead plant material, which is easily spread by wind.

Many other examples of airborne contact dermatitis are published

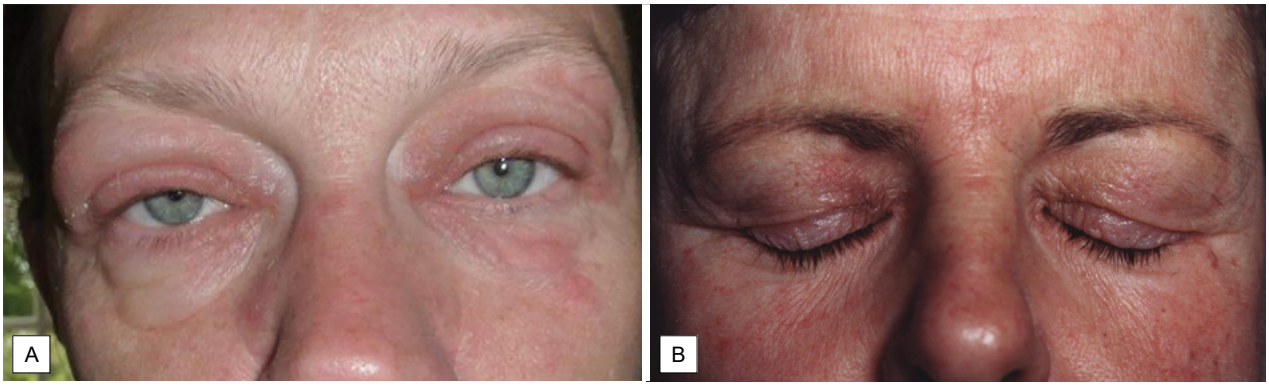

Figure 1 Examples of periorbital allergic contact dermatitis from airborne exposure to MI

TABLE 1

Most common causal agents of airborne-induced allergic contact dermatitis found in the literature from 2007-2011

Agents	No. of patients
Drugs	43
Budesonide	16
Plants	42
Fewerfew	12
Plastic, glue components	37
Epoxy resin	22
Preservatives and other chemicals	21
MCI/MI	10
Metal salts	12

as case reports with many different allergen exposures based on patient history, distribution pattern of the dermatitis, patch testing and follow-up afterwards, i.e. pharmaceutical chemicals in production plants, metals, fungicides and latex.

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3k

CONTACT DERMATITIS: HEMATOGENIC SYSTEMIC CONTACT DERMATITIS

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KEY MESSAGES

- In the absence of cutaneous contact allergen exposure, recurrent symmetrically distributed eczema, vesicular hand dermatitis, papular-pruritic dermatitis and "flare-up" at sites of previous dermatitis are suspect of SCD
- Typical elicitors are metals, allergens of plant origin and drugs
- After respective diagnosis allergen avoidance for example by dietary strategies is important
- Future research is needed to characterize individual proneness to SCD and to develop novel treatment strategies

INTRODUCTION

Systemic contact dermatitis (SCD) is a form of delayed type (type IV) hypersensitivity that occurs in sensitized individuals upon exposure "from inside the body" to contact allergens. Such hematogenic exposure happens both in daily life for example to food constituents and under selected conditions i.e. upon drug administration or from sources in the organism like metal releasing implants. Typical elicitors of SCD are i) metals like nickel, cobalt, chromium or gold, ii) substances of plant origin like balsam of peru, propolis, sesquiterpene lactones, oleoresins, iii) food additives like aspartame and iv) drugs. Patients often do not recognize the correlation between recurring symmetric dermatitis/vesicular eczema lesions, intake of "hidden" allergens (by nickel-/chromate-rich food, sesquiterpene lactones in spices, herbs or aspartame-sweetened foods) and respective contact allergy (Figure 1).

PATHOPHYSIOLOGY

The central aspect is T-cellular delayed type hypersensitivity to haptens the patient has previously been sensitized with. Observations in favour of this are: biopsy often shows lymphohistiocytic infiltrates and eosinophils; provocation test with the culprit allergen can reproduce the symmetric lesions often even with recurrence in same location; drug-/hapten specific T-lymphocyte proliferative and cytokine reactivity *in vitro*; cytokine profiles reflecting TH1 pattern, but also giving link to eosinophil-rich inflammation by TH2 (IL-4, IL-13, IL-5) cytokines; existence of not only circulating and skin immigrating but also local, i.e. skin–resident memory T-cells; proof of allergen-induced IL-17 and IFN-γ secretion by skin resident memory $CD8^+$ T cells. Individual factors predisposing to SCD are still under investigation.

CLINICAL PRESENTATION

Already in 1990 F Klaschka and J Ring reported on "systemically induced contact eczema". Eczema lesions in the absence of local cutaneous exposure might indicate SCD. Recurrent vesicular hand dermatitis, symmetrically distributed nummular but also papular-pruritic dermatitis and "flare-up" at sites of previous dermatitis is suspect of SCD. Some authors also include vasculitic lesions in the spectrum of SCD. Acral, anogenital and flexural erythema and dermatitis – as well as erythema multiforme like eruptions – are often related to drug hypersensitivity. Other drug related reactions are SDRIFE (symmetrical drug-related intertriginous and flexural exanthema) or baboon syndrome and DRESS (drug reaction with eosinophilia and systemic symp-

TABLE 1

Example of Nickel and Balsam of Peru avoidance diet	
Nickel-free dietary recommendations	**Balsam of Peru-free dietary recommendations**
To avoid:	**To avoid:**
• Fish (pike, herring, sardine) • Sea food, crustaceans • Nuts, legumes (beans, lentils, soy, peanuts, peas) • Lettuce, cabbage • Chocolate • Hard cheese • Whole grain flour, brown rice • Fruits (ananas, fig, cherry, peach, banana)	• Citrus fruits • Tea, tobacco with aromated flavour • Food with aromated flavour (ice cream, sweets, cookies, chewing gum) • Coke and other lemonades • Fragrance like Isoeugenol (Tooth paste) • Spices (vanilla, cinnamon, curry, clove)

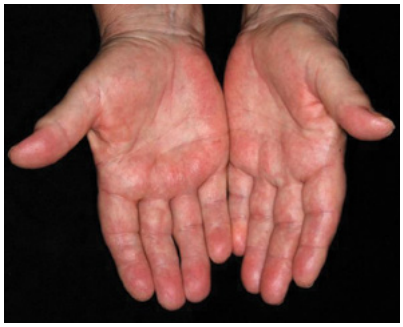

Figure 1 Vesicular, dyshidrotic hand eczema in a chromate allergic patient after insertion of chromium-containing and releasing arthroplasty

toms). Manifestation of SCD may go along with not always specific extracutaneous findings like fatigue, headache, gastrointestinal symptoms. Accordingly, data on extracutaneous symptoms are not conclusive and respective controlled studies are missing.

MANAGEMENT

Diagnosis of SCD consists of ruling out other skin disease, careful history, allergy tests in particular patch testing to allergens in question and provocation. For example in the case of nickel- or chromium-allergy, not only food-related ingestions (like tea, cereals, fish) but also a smoking habit and metal implants could be source of exposure. In the case of cutaneous signs and symptoms clinical relevance is strengthened if provocation test does reproduce SCD – for example by oral provocation with balsam of Peru, chromium or nickel. Apart from therapy of acute dermatitis – if necessary even by oral corticosteroids -, allergen avoidance is mandatory. With respect to food-related SCD effectiveness of for example nickel avoidance diet has been reported in particular if causal link was shown by preceding oral provocation (Table 1). "General" usefulness of dietary treatment is however still controversial. Systemic contact dermatitis related to metal implants is rare and relation to allergy difficult to prove. Treatment strategies (like removal of osteosynthesis material, use of alternative materials including surface coated implants) for such persisting implant related symptoms should always be planned together with the treating surgeons. For SCD in general, studies are needed to better characterize both symptoms and their causal link to allergen exposure. Further treatment strategies are still under investigation like the recently suggested Dupilumab-therapy for blocking the TH2 axis in contact dermatitis.

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31 CONTACT DERMATITIS: OCCUPATIONAL CONTACT DERMATITIS AND PREVENTION

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KEY MESSAGES

- Occupational contact dermatitis (OCD) is one of the most frequent occupational diseases, however, it is underestimated and under-recognised
- A decrease in the prevalence of OCD in recent years due to the improvement of preventive measures in companies has been reported
- Accurate diagnosis of OCD relies on meticulous history taking, thorough physical examination, careful assessment of possible work-related contact allergens and irritants, and comprehensive patch testing to confirm or rule out allergic sensitization
- Therapy consists in the treatment of dermatitis as well as on preventive measures

DEFINITION

The medical definition of the Occupational Contact Dermatitis (OCD) is "any skin, mucous or annexes alteration, directly or indirectly caused, conditioned, maintained or aggravated by whatever substance used in the occupational activity or existing in the workplace". The extent of these diseases is limited by the legislation of each country that regulates according to social and economic aspects which are considered in practice OCD.

EPIDEMIOLOGY AND MANIFESTATIONS

There are no rigorous studies on the prevalence of OCD; it also varies according to the occupation performed. Occupational skin diseases are ranked among the top five occupational diseases in many countries. The literature suggests that contact dermatitis accounts for 90-95% of all reported occupational skin diseases.

The most reliable studies estimate the incidence to be between 11 - 86 cases per 100 000 workers per year, but official statistics would be underestimated due to non-notification (mild cases) or no evaluation of them due to job changes or loss of employment.

In recent years, there has been a decrease in the incidence of OCD that might be related to improvements in working conditions, but that also may be influenced by reduced reporting of new cases.

Overall irritant OCD (cumulative exposure to chemical agents, physical irritants, wet-work...) occurs more commonly than allergic OCD (Table 1).

In 80-90% of the OCD there is an affectation of the hands.

HIGH-RISK OCCUPATIONS

Among the professions most affected in relation with OCD are: agriculture, carpentry, construction, photography and graphic arts, food handlers, hairdressing, bakery, painting, veterinarians, health workers, dental technicians and automotive, footwear, ceramics, electronics, pharmaceutics, footwear, metallurgy, textile, chemistry industries.

But in recent years cases of OCD have been published in relation to other professions less well studied (Table 2).

DIAGNOSIS

A cautious and meticulous history, physical examination and allergy testing has to be taken when diagnosing OCD. The diagnosis is based on several factors, such as

TABLE 1

Common occupational contact irritants and allergens

IRRITANTS	ALLERGENS
Acids and alkalis	**Metals**
Solvents	Nickel, chromium, cobalt, mercury, gold, platinum
Aliphatic: petroleum, kerosene, gasolina	**Rubber additives**
Aromatic: benzene, toluene, xylene	Accelerators: mercaptobenzothiazole, carbamates, thiurams, thioureas
Halogenated: chloroform, trichloroethylene, methyl-chloride	Antioxidants: N-phenyl-N-isopropyl-paraphenylene-diamine, etc.
Miscellaneous: water, alcohols, ketones, glycols, turpentine	**Plastics and resins**
Soaps and detergents	Epoxy, phenolic and acrylic monomers
Plastics and resins	Amine, anhydride, and peroxide catalysts
Epoxy, phenolic and acrylic monomers	Colophony, turpentine, catechols
Amine catalysts	**Biocides**
Styrene, benzoyl peroxide	Formaldehyde and formaldehyde releasers
Metal salts	Glutaraldehyde
Nickel, chromium, cobalt, platinum, arsenic	Isothiazolinones
Plants	Methyldibromoglutaronitrile
Bristles, thorns	Iodopropynyl butylcarbamate
Calcium oxalate: dieffenbachia, philodendron, daffodil, agave	**Cosmetics**
Phototoxic psoralens: Apiaceae, Rutaceae	Paraphenylenediamine
Particles	Glyceryl thioglycolate
Sand, sawdust, fiberglass, metal filings, etc.	Cocamidopropylbetaine
	Parabens and other preservatives (see biocides)
	Fragrances and essential oils
	Plants
	Penta- and heptadecylcatechols
	Sesquiterpene lactones

Sasseville, 2008

a detailed history. In occupational contact dermatitis, there are work-related deteriorations and improvement of skin lesions when off work, such as at weekends and in vacation. This has to be differentiated from non-work-related spontaneous exposure. Also, the patient cooperation has to be assessed, as sometimes there may be a pursuit for secondary illness gain (Figure 1). A systematic clinical examination does confirm the diagnosis of a typical contact dermatitis and lesions at sites of contact to the culprit allergens. Complete information of the place and circumstances of work (workplace survey) helps to assess allergen exposure and study of Material Safety Data Sheets is mostly required. Patch tests are performed for detecting contact sensitizations and the results of the patch tests have to be critically interpreted for their clinical relevance. Furthermore, the course of the illness can be observed in regard to work-related exposure to allergens.

TREATMENT AND PREVENTION

The medical treatment is similar to other forms of contact dermatitis with corticosteroid creams or

TABLE 2

Occupational Allergy Contact Dermatitis due to classic and new contact allergens in lower risk occupations		
Occupation	**IN CONTACT WITH...**	**HAPTEN**
Laboratory technicians	Microscopy immersion oil	Epoxy resin
Milk industry employee	Milk cartons (inks)	Paraphenylendiamine
Stewardess	Sky blue uniform	Disperse blue dyes
Repair of car doors	Adhesive	Nitromethane
Obstetrician and gynecology resident	Operating room surgical mask	Thiuram
Pro shop operator bowling alley	Bowling balls	Epoxy resin
Golfer (Handicap 5.2) and golf club repairman	Glue, golf sticks	Epoxy resin
Bartender	Lime peel	Geraniol
Teacher of "polychrome and golden frame and wooden opuses restoration"	Dust gilding	Gold (airborne CD)
Olympic gymnastic athlete	Leather wrist support	Dichromate potassium
Horse trainer	Syringe with the drug for gastric ulcer	Omeprazole
Woodworker	Ornamental wooden box	Ebony wood
Wine-making industry	Wine	Potassium metabisulfite
Pizza makers	Garlic	Diallyl disulfide
Windscreen repairer	Adhesion promoter solution	(3-mercaptopropyl) trimethoxysilane
Manufacturing and packing scratchcards	Lottery scratchcards	Nicquel
Pig farmer	Veterinary powder	Vit. K3 sodium bisulphite
Pastry chef	Limes	Limes peel (Protein contact dermatitis)
Quality control unit in a potato chips factory	Spices and potato chips	Capsaicin
Physiotherapist	Massage products	Polyethylene glycol-7 monooleate
Boat builder	Glues	Epoxy resin
Flamenco guitarist	Acrylate nails	Methacrylates
Fast-food restaurant	Cleanser	Sodium cocoamphopropionate
Otorhinolaryngologist	Otomicroscope	Antioxidants in black rubber
3D printer	Plastics used with the printer	Epoxy resin
Cheese counter assistant	Cheese	Dodecyl gallate
Hockey player	Shin pads	Acetophenone azine
Gynaecologist	Ultrasound gel	Methylisothiazolinone
Uber driver	Perfume diffuser	Fragances
Professional football player	Plasters to tightly fixate his socks	Colophonium
Boat upholsterer	Glue	Colophonium
Marine engineer	Machine oil	Cobalt

Source: Contact Dermatitis and Dermatitis Journals (2000-19)

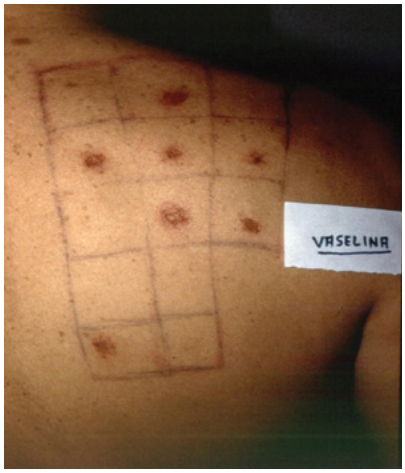

Figure 1 Facticious disorder imposed on self (Compensation neurosis). Alterations of patch tests by the patient using caustic soda to simulate an allergic OCD, including positivity of the negative control (petrolatum). Photo courtesy of Dr. Antonio Parra

TABLE 3

Measures for prevention of occupational contact dermatitis
Primary prevention:
Pre-employment screening (controversial)
Worker education
Use of suitable gloves and other personal protection equipment
Periodic inspection of fulfillment of protection measures
Automatisation of industrial processes
Change of potential irritant or sensitizer substances
Use of barrier creams (controversial) and moisturizers
Cutaneous hygiene
Avoid prolonged contact with well-known irritant or sensitizer allergens
Secondary prevention
Change of job or work process
Abandonment of their work activity (assessment of compensations, disabilities...)
Tertiary prevention
Rehabilitation and reintegration to work

ointment, basic emollient therapy, phototherapy, sometimes oral medications (antihistamines, oral corticosteroids) and preventive measures. The itching associated with acute contact dermatitis is often severe and is usually best treated by steroids rather than by antihistamines, that have no documented effect on dermatitis. There are three levels of prevention for OCD (Table 3). Primary prevention aims to prevent disease or injury before it ever occurs, secondary prevention to reduce the impact of ACD and tertiary prevention to soften the impact of ACD on lasting effects.

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4 PHOTOCONTACT DERMATITIS AND PHOTOALLERGIC REACTIONS

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PHOTOCONTACT DERMATITIS

Reactions involving a sensitizer and ultraviolet radiation can be distinguished between phototoxic and photoallergic reactions. Phototoxic reactions are obligatory in contact with the sensitizer and show a dose-dependency. Usually phototoxic reactions are described with sharply demarcated reddening, painful burning and sometimes with blister formation. The reaction usually occurs with some latency and heals with long lasting hyperpigmentation.

In contrast to this, photoallergic contact dermatitis is a delayed-type hypersensitivity cutaneous reaction in response to a photoantigen applied to the skin in previously sensitized patients. A photo-activated substance behaves as a hapten and elicits an immunologic response. Clinically it is identical to an allergic contact dermatitis. The reaction is usually dose-independent and the developing erythema un-sharply demarcated (so-called spreading reaction).

The recommended European photopatch test baseline series contains mainly ultraviolet filters and drugs, mostly non-steroidal anti-inflammatory drugs.

KEY MESSAGES

- Photocontact dermatitis is a delayed-type hypersensitivity cutaneous reaction in response to a known photoantigen
- A photopatch test using standardized allergens should be performed in order to find the eliciting photoallergen
- Polymorphous light eruption is a common delayed hypersensitivity reaction to a hitherto unknown endogenous photoallergen and can be confirmed by phototesting
- Solar urticaria is an immediate hypersensitivity reaction triggered by uncharacterized chromophores and light, which can be confirmed by phototesting

The agents are applied in duplicate on the mid upper back skin on either side of the vertebrae. After 24 or 48 hours one side of the patch test is removed and the skin is irradiated with 5 J/cm^2 broad-spectrum UVA. The other side remains unirradiated and serves as control (Figure 1). The reactions are read immediately and after 48, 72 and

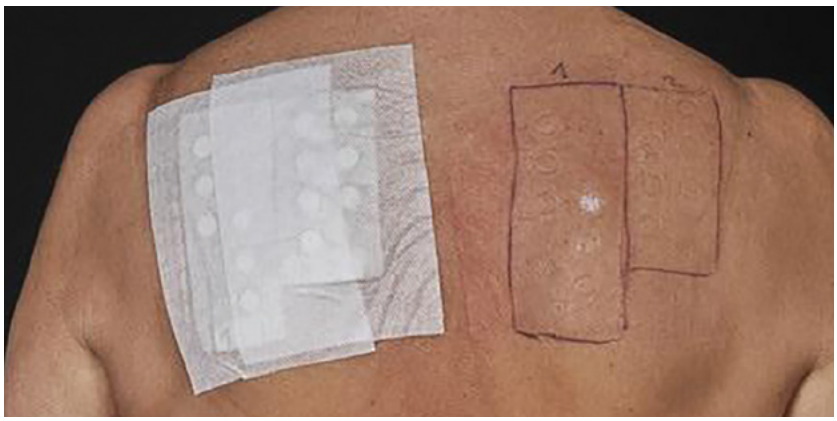
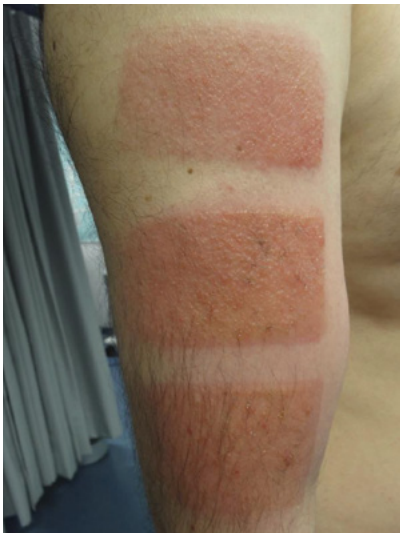


Figure 1 Photopatch test on day 2 (left side: unirradiated control, right side: irradiation with 5 J/cm^2 UVA)



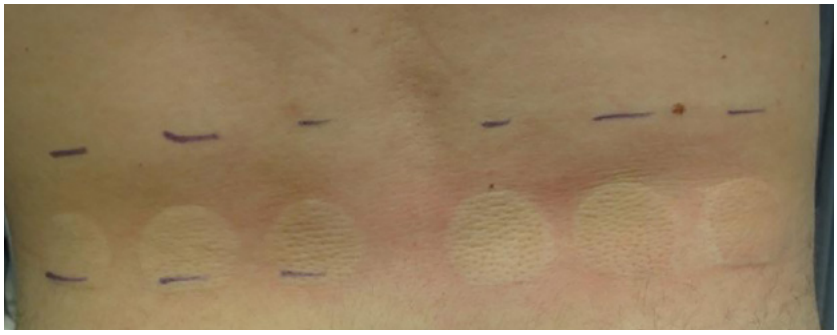


Figure 3 Photoprovocation test for solar urticaria (upper row: stepwise UVB exposure with negative results after 20 minutes; lower row: stepwise UVA exposure with positive results after 20 minutes)

Figure 2 Photoprovocation test for polymorphous light dermatitis (upper field: application of 1.5 MED-UVB on three consecutive days, middle field: application of 1.5 MED-UVB and 100 J/cm^2 UVA on three consecutive days, lower field: application of 100 J/cm2 UVA) on three consecutive days; reading with positive reaction 24 h after the last irradiation)

96 hours, after irradiation and recorded using the International Contact Dermatitis Research Group scoring system.

Detection of crescendo or decrescendo scoring patterns suggests allergic and non-allergic mechanisms, respectively.

PHOTOALLERGIC REACTIONS

Polymorphous light eruption (PLE) is the most common form of immunologically mediated photosensitivity disorders. A delayed hypersensitivity reaction to an endogenous antigen expressed after exposure to ultraviolet radiation is postulated. Typically the itching lesions appear several hours after intense UV-irradiation in the spring or during the first days of a holiday in the sun. Predilections sites are the lower arms, the back of the hands and the décolleté. The morphology ranges from papules to papulovesicles to EEM-like lesions.

For phototesting UV-sources with broadband UVB and UVA are necessary. On day 1 the minimal erythema dose (MED) is defined. On day 2, 3 and 4 1.5 MED-UVB is applied on one field (8 x 5 cm), 100 J/cm^2 UVA on a second field and the combination of both in a third field of an area usually affected by the disease. The reactions are read each day and 24 h after the last irradiation (Figure 2).

Solar urticaria is a relatively rare IgE-mediated type of physical urticaria triggered by uncharacterized chromophores. Within several minutes after sun exposure wheal and flares, sometimes only an itching erythema develops which fades within the next hours.

Testing is done by stepwise UVB and UVA exposure on UV-unexposed skin and by a 10 min provocation with visible light. The reading is done immediately and after 20 min (Figure 3).

The knowledge about the procedure and interpretation of the phototesting allows the physician to make the correct diagnosis and to initiate adequate therapy measures.

Recommended therapies are shown in Table 1.

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TABLE 1

Therapy of photocontact dermatitis, polymorphous light eruption and solar urticaria

Disease		Treatment
Photocontact dermatitis	First-line therapy (acute flare)	• Topical/systemic corticosteroids
	First-line therapy (prevention)	• Avoidance of photoallergen and/or sun exposure
Polymorphous light eruption	First-line therapy (acute flare)	• Topical/systemic corticosteroids
	First-line therapy (prevention)	• Moderation of sun exposure • High-factor broad-spectrum sunscreens (containing antioxidants) • Clothing photoprotection • Avoidance of artificial tanning devices in more severe cases
	Second-line therapy (prevention)	• Narrowband UVB phototherapy • PUVA • Systemic antioxidants • Cyclosporine • Azathioprine
Solar urticaria	First-line therapy (prevention)	• High-factor broad-spectrum sunscreens • Clothing photoprotection • Oral antihistamines
	Second-line therapy (prevention)	• Hardening/Desensitization with phototherapy (UVA, narrowband UVB or PUVA) • Omalizumab • Cyclosporine • Azathioprine • Immunoglobulins • Plasmapheresis

5a CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: DRUG-INDUCED ANAPHYLAXIS AND URTICARIA

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INTRODUCTION

Drug hypersensitivity reactions (DHRs) are a prevalent phenomenon and affect more than 7% of the population, with the skin as the most frequently involved organ. Immediate reactions (IDHR) usually appear within 1-6 hour after drug administration, with anaphylaxis and urticaria as the main clinical manifestations.

KEY MESSAGES

- The skin is the organ most frequently involved in DHR
- Drug Hypersensitivity reactions can be immunologically and non-immunologically mediated
- Urticaria and anaphylaxis are frequent clinical manifestations of DHRs
- Drug provocation test is the gold standard in drug allergy diagnosis

UNDERLYING MECHANISMS

Immunological mechanism: Anaphylaxis and urticaria are usually mediated by specific IgE (Figure 1), whose binding to the FcεRI receptor on mast cells and basophils leads to degranulation and release of preformed mediators that cause the clinical symptoms. The most frequent culprits are beta-lactam antibiotics.

Non-immunological mechanism: Anaphylaxis and urticaria can also be mediated by a pharmacological mechanism (Figure 2), with non-steroidal anti-inflammatory drugs being the most frequent culprits.

CLINICAL PRESENTATION

Anaphylaxis is a severe systemic DHR characterised by rapid onset of bronchospasm, hypotension, tachycardia or gastrointestinal symptoms and in most cases associated with urticaria. Urticaria is characterised by the appearance of itching hives anywhere in the body that disappear within 24 hours (Figure 3). In half of the cases it is accompanied by a deeper oedema of the skin or mucosa called angioedema.

DIAGNOSTIC APPROACH

A complete clinical history is important to determine whether the reaction is suggestive of an IDHR or not. It may include information about clinical symptoms, date of the reaction, time interval between drug intake and reaction onset, suspicious drug, and the presence of any other drug. Information about underlying conditions and the need to continue the treatment are also important.

Skin test (ST) is the best-validated method in IgE-mediated reactions (Figure 4), and, if negative, a drug provocation test (DPT) is necessary for confirming the diagnosis. In non-immunologically mediated reactions, DPT is the only available tool. In IgE-mediated DHR, *in vitro* tests, such as basophil activation test or specific IgE determination by immunoassay, are promising diagnostic tools especially in patients with severe reactions.

MANAGEMENT

Stopping the culprit drug administration and treating acute symptoms are the first steps. In case of anaphylaxis, intramuscular adrenaline is the first-choice treatment and it has to be used as soon as possible. Antihistamines and corticosteroids can be used in both anaphylaxis and urticaria.

If the patient needs to continue the treatment, a non-cross-reac-

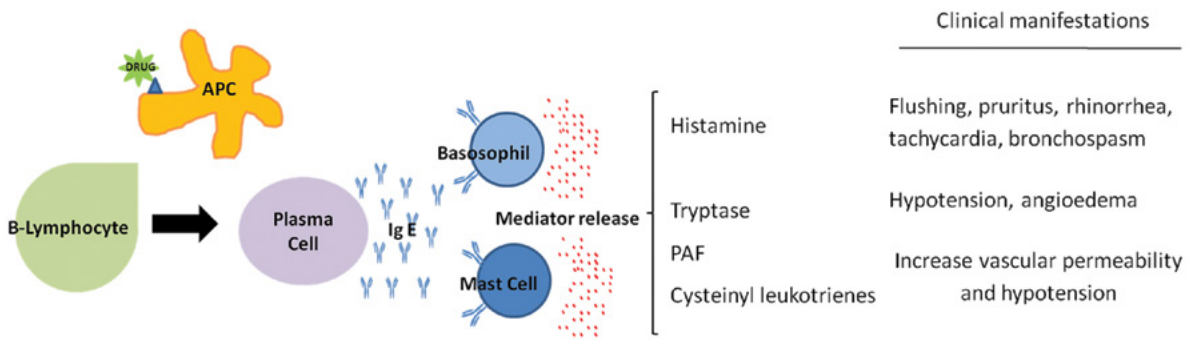

Figure 1 Immunological mechanism in IDHRs. Mediator released and the associated clinical manifestations

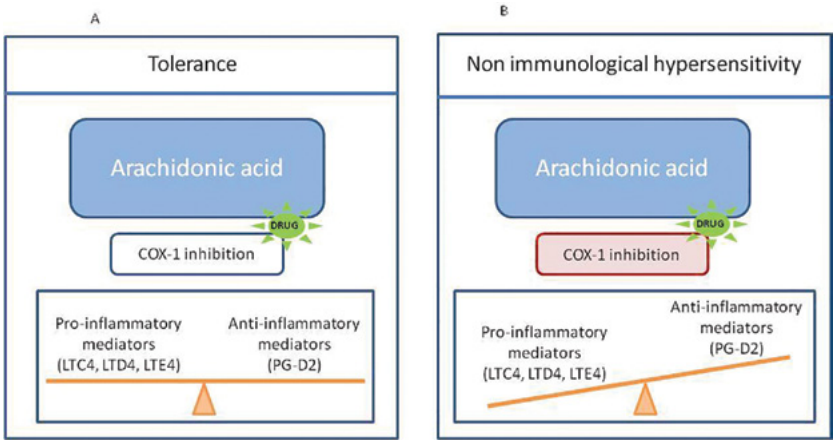

Figure 2 Figure 2 (A) Arachidonic acid metabolism in presence of NSAIDs in general population, (B) Arachidonic acid metabolism in presence of NSAIDs non immunological hypersensitivity

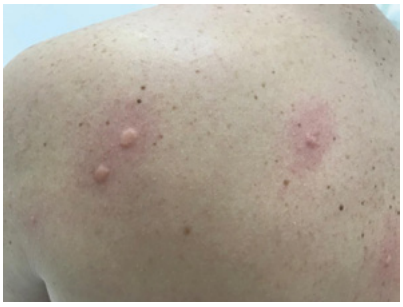

Figure 3 Acute urticaria due to acetyl salicylic acid

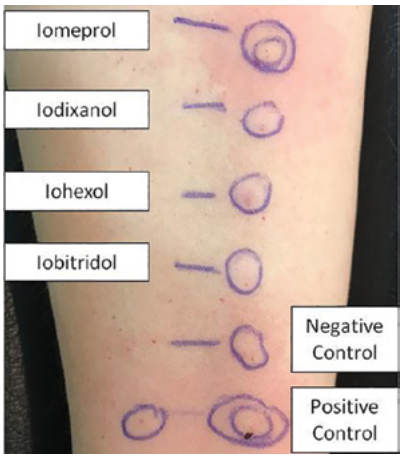

Figure 4 Iodated contrast media skin test. Positive intradermal test to Iomeprol

tive drug must be chosen. If this is not possible and drugs from the same pharmacological group are necessary, tolerance must be checked before. When there are no alternatives a desensitisation process can be done.

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5b CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: MACULOPAPULAR (MEASLES-LIKE) EXANTHEM

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KEY MESSAGES

- Exanthem is a stereotypic reaction pattern of the skin, an inflammation of the papillary dermis and the superficial vascular plexus. Various agents, such as viruses, bacteria, allergens (e.g. drugs) or autoantigens may lead to the same clinical and histological picture
- A maculopapular or measles-like exanthem is the most common clinical manifestation of drug allergy
- On the other hand, drugs may be unjustifiably blamed for triggering an exanthem that has an infectious cause
- Patients with a history of drug-associated exanthem should be subjected to allergy testing for definitely confirming or ruling out drug hypersensitivity

The term exanthem refers to a group of infectious and non-infectious, inflammatory skin diseases with a dynamic course and a quite heterogeneous clinical morphology. Characteristic are the acute onset and the relatively rapid healing, i.e. an exanthem is always limited in time. The macular, papular, papulovesicular, petechial (hemorrhagic) or pustular single lesions are more or less generalized or disseminated and are distributed symmetrically. Typically, there is a relative sparing under pressure areas, as seen in Figure 1.

Exanthem is a stereotypic reaction pattern of the skin, an inflammation of the papillary dermis and the superficial vascular plexus. Alterations in the epidermal compartment are secondary. Various agents, such as viruses, bacteria, allergens (e.g. drugs), autoantigens, toxic metabolites or activated T cells (during GvHD) lead to the same histological and clinical picture (Figure 2). Therefore, evaluation of a skin biopsy specimen is of limited value in differentiating drug-induced exanthem from e.g. viral exanthem. Patients with a history of drug-associated exanthem should be subjected to allergy testing for definitely confirming or ruling out drug hypersensitivity.

A maculopapular or measles-like exanthem is the most common clinical manifestation of drug allergy. If liver and kidney parameters remain within their normal range, the term uncomplicated drug-induced exanthem may be used (Table 1). On the other hand, drugs may be unjustifiably blamed for triggering an exanthem that has an infectious cause (Figure 1). This is quite understandable, given that the rash, which is equally impressive for both sides, physician and patient, occur suddenly and in temporal relationship with the intake of e.g. an antibiotic. However, antibiotics are prescribed because of febrile infectious diseases, which are often accompanied by an exanthem.

For allergists investigating drug reactions, the clinical differential diagnosis of exanthem is an ongoing challenge (Table 2). The allergist has generally not seen the skin reaction himself, his retrospective assessment relies on reports, patient descriptions and, at best, photographs nowadays sometimes taken by the patient himself using e.g. a smartphone. General complaints, clinical findings, course and morphology of the various exanthematous skin diseases may give important diag-

TABLE 1

Comparison between uncomplicated maculopapular exanthem, hypersensitivity syndrome and severe bullous skin reactions - In an individual case, a suddenly appearing maculopapular exanthem can quickly proceed to a more severe drug reaction. A measles-like exanthem may be the earliest sign of a hypersensitivity syndrome or a bullous drug reaction, the full clinical picture develops within a few hours to a few days

	uncomplicated exanthem	drug-induced hypersensitivity syndrome	Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)
time interval between onset of drug intake and appearance of first skin lesions	a few hours to a few days	a few hours to several weeks	a few days to several weeks
skin symptoms	measles-like (maculopapular) exanthem	picture either comparable to uncomplicated exanthem or e.g. pustular exanthem, erythroderma, erythema multiforme-like lesions	initially inconspicuous exanthem, the clinical picture of the SJS-TEN spectrum develops within a few hours to a few days SJS: atypical target lesions TEN: blisters and erosions
subjective skin complaints	itch	itch, burning	pain
facial erythema, and edema	(+)	+++ (quite typical sign)	+++
fever episodes	(+)	++ (flu-like symptoms)	
involvement of internal organs	none (by definition), negligible hepatitis	hepatitis, interstitial nephritis, generalized enlargement of lymph nodes	arterial hypotension, lung failure, renal insufficiency, hepatitis
mucosal lesions	–	(+)	+++ (conjunctiva, oral and genital mucosa)
laboratory signs	normal findings (by definition), possibly eosinophilia, minimally elevated liver enzymes	often eosinophilia > 1500/µL, atypical lymphocytes, liver enzymes >2× ↑, lactate dehydrogenase ↑	granulocytopenia, liver enzymes ↑
skin histology	the various exanthematous reactions are indistinguishable, exanthem is a stereotypic reaction pattern of the skin		complete necrotic epidermis is a defining symptom of the SJS-TEN spectrum
mortality	near 0%	up to 10%	SJS: 1–5%, TEN: > 30%
causal drugs	aminopenicillins, sulfonamides	anticonvulsants, sulfonamides, antiretroviral drugs, allopurinol	
differential diagnosis	viral exanthem, autoimmune diseases, GvHD, syphilis	viral exanthem, pustular psoriasis, erythema multiforme	staphylococcal scalded skin syndrome, generalized fixed drug reaction, GvHD, bullous autoimmune diseases, toxic shock syndrome
treatment	discontinue causal drug (treating through in case of therapeutic necessity), topical glucocorticoids, H_1 antihistamines	discontinue causal drug, 1 mg of prednisolone/kg for 3-5 days, then slow dose reduction (often prolonged healing over several weeks)	discontinue causal drug, inpatient supportive therapy, intensive care or burn unit if necessary
remarks	skin testing and/or laboratory testing with the causal drug may yield positive results	reactivation of herpes viruses: HHV-6, HHV-7, CMV (HHV-5), EBV (HHV-4)	patients at risk: older patients with malignancy, brain cancer, radiotherapy, etc.
genetic disposition	not known or without clinical relevance	first degree relatives of patients with hypersensitivity syndrome or SJS/TEN have an increased risk of developing these conditions compared to the normal population	

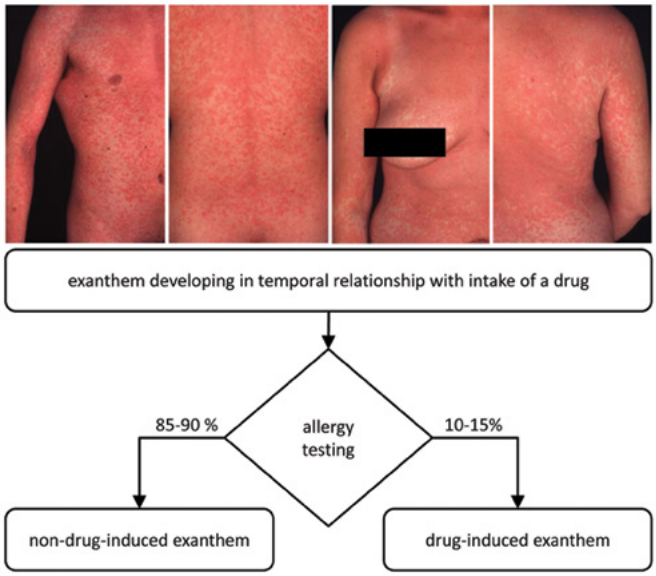

Figure 1 Based on temporal relationship alone many patients with exanthem are incorrectly labelled as being drug allergic - The principal diagnostic problem is the differentiation between drug-induced exanthem and viral or bacterial exanthem, because both disorders may cause a clinically indistinguishable skin reaction. Several studies in specialized allergy units identified drug allergy in only approximately 10 to 15% of patients with a suspected drug reaction

TABLE 2

Comparative features of drug-induced exanthem and infectious exanthem - Most clinical signs are common to both conditions, only some selected forms of viral exanthem have a rather specific clinical pattern. Respiratory or flu-like symptoms favor the diagnosis of an infectious exanthem. Importantly, these complaints are concurrently the reason for intake of drugs, e.g. antibiotics

	drug-induced exanthem	viral or bacterial exanthem
history	temporal relationship to drug intake	respiratory symptoms, flu-like symptoms
common signs	generalized maculopapular exanthem, itching, slightly elevated hepatic transaminases, healing with fine desquamation	
specific signs	none	e.g. Gianotti-Crosti syndrome, Koplik spots (measles), enlarged tonsils (infectious mononucleosis)
diagnostics	allergy testing	bacteriology, serology

nostic clues. Certain skin lesions, such as small bleeding (petechiae) and blisters (papulovesicles), involvement of hands and feet as well as mucosal enanthem favor the diagnosis of a viral exanthem.

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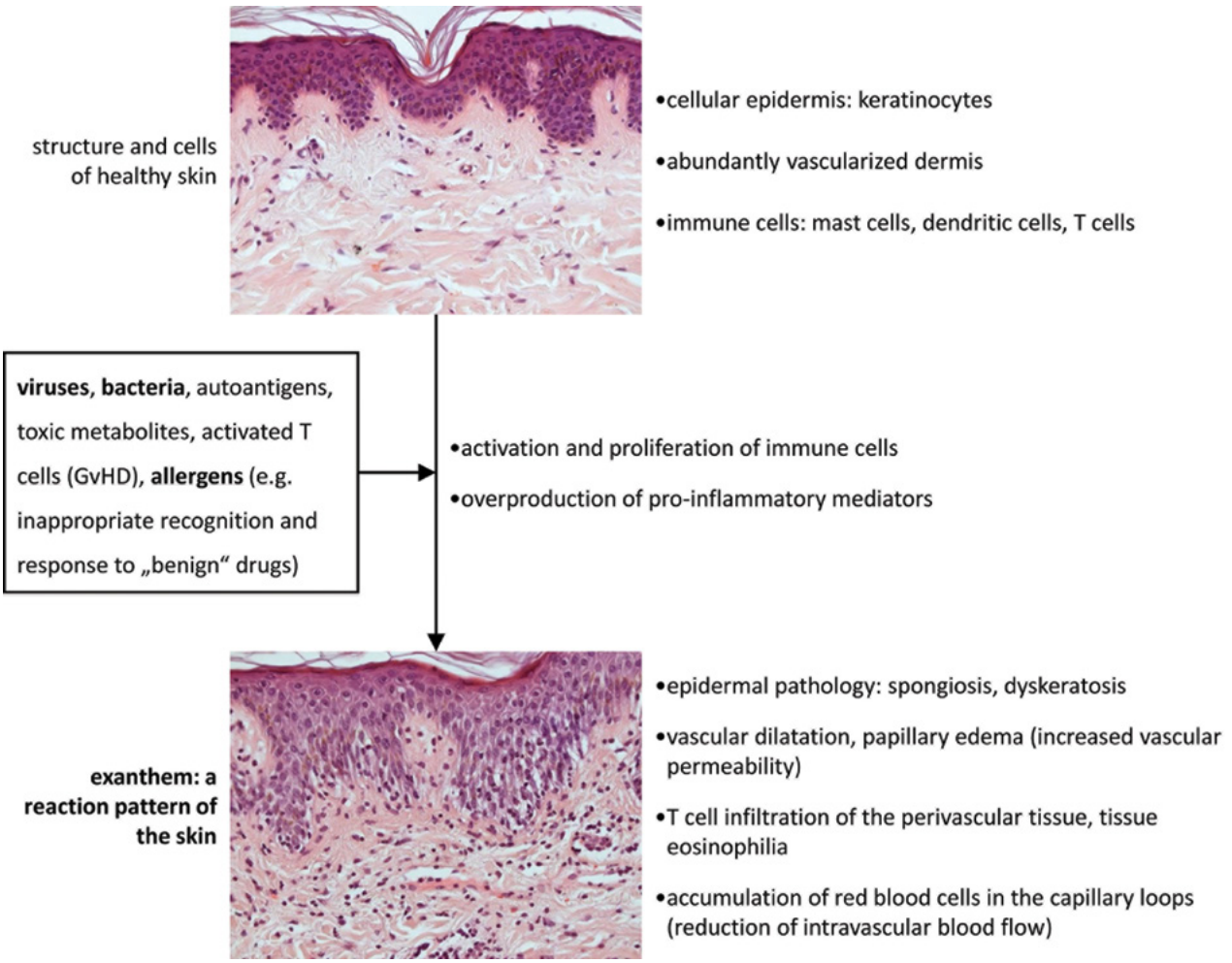

Figure 2 Exanthem is an inflammation of the superficial reactive unit of the skin, the papillary dermis and the superficial vascular plexus - The skin of humans contains many immune cells to protect us against microorganisms. The fine-tuned skin immune system may become dysregulated, allergens (e.g. drugs) or autoantigens inappropriately activate immune cells leading to exanthem

5c CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: SYMMETRICAL DRUG RELATED INTERTRIGINOUS AND FLEXURAL EXANTHEM (SDRIFE)

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KEY MESSAGES

- SDRIFE is a benign drug eruption manifesting primarily in the great folds
- SDRIFE may occur upon first exposure to the drug
- Beta-lactam-antibiotics and other anti infectious agents are the most common elicitors
- Skin tests and cellular activation tests are mostly negative, re-exposure leads to an identical exanthema in most cases

INTRODUCTION

The term "Symmetrical drug related intertriginous and flexural exanthem" (SDRIFE) describes an uncommon, benign drug eruption with a peculiar distribution pattern and has been proposed in 2004 by Hausermann et al. to differentiate this clinical entity from other forms of cutaneous adverse drug eruptions (CADR). It is distinct from Baboon-Syndrome (BS) or other forms of systemic allergic contact dermatitis (SCD) by being predominantly, but not exclusively caused by systematically applied anti-infective drugs, usually without prior cutaneous sensitization, whereas in BS and classical systemic contact allergy, allergens such as metals, plants, herbals and topical medicaments are typical elicitors after previous cutaneous sensitization.

CLINICAL PRESENTATION

SDRIFE affects the perianal and perigenital area in a V-shaped form and at least one other flexure, such as the axillae, popliteal fossae, crook of the elbow and frequently the neck. It usually presents with an erythema, but pustular, papular or bullous variants and targetoid lesions have been described (Figure 1-3). Sometimes erythema of the interdigital space or submammary folds can also be found. Patients are usually in a good general condition and systemic signs of inflammation, blood cell dyscrasia or organ involvement are generally not found. Histology cannot clearly differentiate between SDRIFE, BS and other, mostly bullous drug eruptions, mainly erythema multiforme or fixed drug eruption.

SDRIFE is distinct from classical Baboon-Syndrome as it does not only affect the gluteal and perigenital area, but involves other major flexures. It is caused by systemically administered drugs without prior contact sensitization, has been described in children from age 18 months, as well as in adults, and there seems to be a male predominance untypical for other drug eruptions. It usually appears within hours to two days after exposure to the causative agent.

DIAGNOSIS

The diagnosis of SDRIFE is made through five diagnostic criteria (Table 1). In contrast to BS, allergologic diagnostic skin tests (patch tests, intradermal tests with late reading), as well as lymphocyte stimulation tests are negative in SDRIFE in the majority of cases. Systemic provocation testing, however, results in an identical exanthema in almost all patients. Histology shows a T-cell mediated reaction corresponding to a type IV hypersensitivity immune response, but is not specific for SDRIFE.

In the differential diagnosis, in addition to BS and SCD, intertriginous mycoses, eczema of the

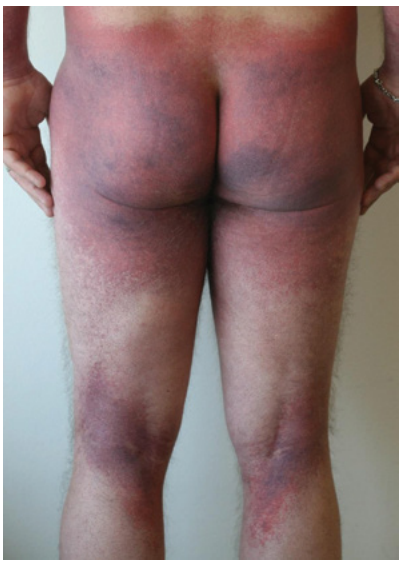

Figure 1 Livid red erythema of the buttocks and the hollows of the knees, after intake of amoxicilline

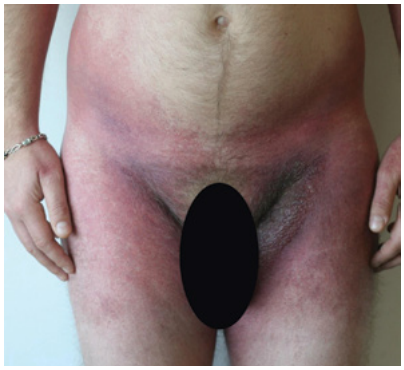

Figure 2 Same patient, V-shaped erythema of the inguinal folds with vesicles and pustules on the left side

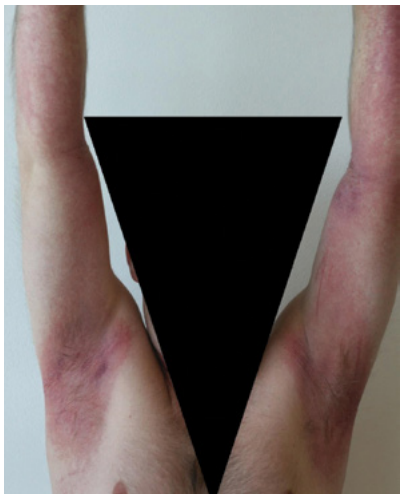

Figure 3 Same patient, erythema of both axillae and elbows

TABLE 1

5 diagnostic criteria for SDRIFE (Hausermann et al. 2004)	
1	Sharply demarcated erythema of the gluteal/perianal area and/or V-shaped erythema of the inguinal/perianal/perigenital area
2	Involvement of at least one other intertriginous/flexural fold
3	Symmetry of affected areas
4	Exposure to systemic drugs at first or repeated dose (contact allergens excluded)
5	Absence of systemic symptoms and signs

flexures, erythematous state of staphylococcal scalded skin syndrome and toxic shock syndrome have to be considered.

TYPICAL ELICITING DRUGS

The most frequently incriminated drugs are beta-lactams, mainly amoxicillin. Many other drug groups have been reported, among them antifungals, antivirals, NSAID, proton pump inhibitors, corticosteroids, radiocontrast media, neuroleptics and antihypertensive drugs.

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5d CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: ACUTE GENERALISED EXANTHEMATOUS PUSTULOSIS (AGEP)

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INTRODUCTION

Acute generalised exanthematous pustulosis (AGEP) is an acute eruption characterised by the sudden onset of numerous non-follicular sterile pustules on an edematous and erythematous background.

KEY MESSAGES

- Acute generalised exanthematous pustulosis (AGEP) usually develops within hours or days of drug exposure
- It typically manifests with dozens to hundreds non-follicular, pinhead-sized pustules on a background of edematous erythema with flexural accentuation
- The histopathological hallmark of AGEP is a spongiform sub-corneal and/or intraepidermal pustules
- AGEP is a self-limiting disease and resolves spontaneously without sequelae

ETIOLOGY AND PATHOGENESIS

AGEP is most often caused by antibiotics, especially aminopenicillins and macrolides; other common culprits include terbinafine, diltiazem, and hydroxychloroquine. There are some reports of AGEP associated with viral, bacterial or parasitic infections. In AGEP, drug-specific $CD4^+$ T cells produce interleukin (IL)-8 and GM-CSF. Both cytokines are involved in tissue accumulation of neutrophils. T helper 17 (Th17) cells are also involved in the recruitment, activation, and migration of neutrophils in AGEP. Mutations in the *IL36RN* gene encoding the interleukin-36 receptor antagonist have been found in a few patients with AGEP.

CLINICAL AND HISTOPATHOLOGICAL FEATURES

The eruption usually develops within hours or days of drug exposure and generally begins on the face or intertriginous areas, and then rapidly extends to the trunk and limbs with a diffuse or patchy distribution. It typically manifests with dozens to hundreds non-follicular, pinhead-sized pustules on a background of edematous erythema with flexural accentuation (Figure 1). The pustular eruption is followed by desquamation with characteristic collarettes of scales. The histopathological hallmark of AGEP is a spongiform sub-corneal and/or intraepidermal pustules. Other common features include edema of the papillary dermis, necrosis of single keratinocytes, and a superficial, interstitial, and mid-dermal inflammatory infiltrate of neutrophils (Figure 2).

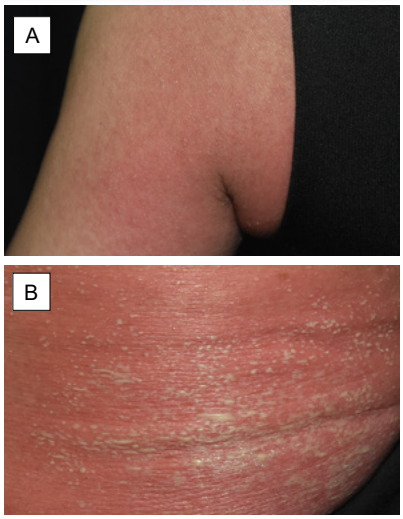

Figure 1 Dozens to hundreds non-follicular, pinhead-sized pustules are noted on a background of edematous erythema with flexural accentuation (A). Pustules on an erythematous base on the right flank (B)

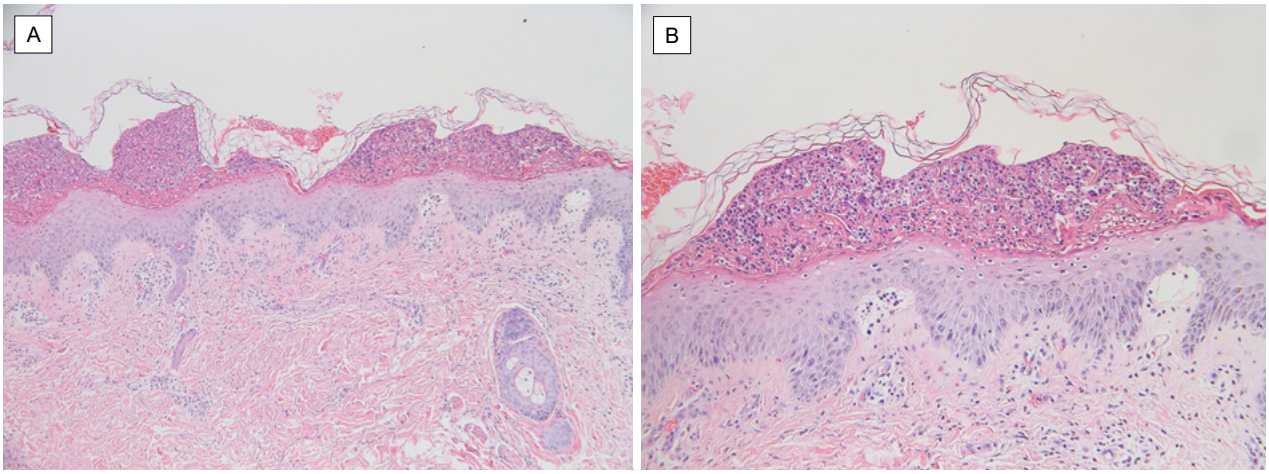

Figure 2 Typical histopathological features of AGEP include spongiform sub-corneal pustules, edema of the papillary dermis, and a superficial, interstitial, and mid-dermal inflammatory infiltrate of neutrophils (A & B)

Eosinophils are often seen in the pustules or dermis.

DIAGNOSIS

Clinical and laboratory criteria for the diagnosis of AGEP are as follows:

- Rapid development of a febrile (≥ 38°C) pustular eruption
- Dozens to hundreds of pinhead-sized, non-follicular pustules on a background of edematous erythema
- Leukocytosis with marked neutrophilia (≥7000/µL)
- Pustular smear and culture negative for bacteria
- Rapid resolution of the rash after drug discontinuation

DIFFERENTIAL DIAGNOSIS

The most important differential diagnosis is generalised pustular psoriasis, because both diseases share common clinical and histological features. Clues that favour a diagnosis of generalized pustular psoriasis include a history of psoriasis, longer duration of fever and pustular eruption, absence of drug exposure, and histologic features combining sub-corneal pustules with acanthosis and papillomatosis. Other differential diagnoses include Stevens-Johnson syndrome/toxic epidermal necrolysis, Sneddon-Wilkinson disease, and bullous impetigo.

MANAGEMENT

AGEP is usually self-limiting, so the management include withdrawal of the offending drug, supportive care, and symptomatic treatment of pruritus and skin inflammation.

PROGNOSIS

AGEP resolves spontaneously without sequelae in most of the patients.

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5e CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

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KEY MESSAGES

- Compared to other drug reactions, DRESS is characterized by a relative long latency time, a protracted course with relapses, and a great variability, also in terms of time, of cutaneous and systemic signs and symptoms
- Particularly in the early stages, DRESS may resemble other diseases and is a diagnosis by exclusion, necessitating appropriate further investigations, including laboratory examinations
- The DRESS-score is aimed at a balanced validation of cutaneous, hematological, organ, and other features, including the course
- Although a causative role of herpes viruses in early DRESS has been speculated on, DRESS is primarily regarded an immune response to the drug, possessing an innate ability to stimulate T-cells
- Early recognition, followed by prompt withdrawal of the culprit drug is the most decisive step to avoid disease progression, thus potentially resulting in less morbidity and mortality and restoring health

The acronym DRESS refers to a severe drug-induced reaction, defined by fever, an extending widespread, polymorphous skin eruption, lymphadenopathy, haematological abnormalities, and visceral involvement, often starting with prodromal flu-like symptoms. Characteristics are an exfoliative dermatitis and facial oedema (Figure 1). Considerable hyperleucocytosis, eosinophilia and atypical lymphocytes are regularly observed. Visceral involvement can be extensive, most commonly of the liver, followed by kidney and lungs, whereas other organs are more rarely affected. Course and time to onset are relatively long. Evolution of signs and symptoms is relatively slow and can present in haphazard combinations, also in time.

DRESS may resemble other diseases and is a diagnosis by exclusion, necessitating appropriate further investigations. Due to the clinical and biological variability, the validation score proposed in 2007 for potential cases, comprising course and clinical and laboratory abnormalities, is nowadays used to establish diagnosis, and is a guideline for features to be investigated during the disease (Table 1).

Relapses may occur after herpesvirus reactivation (especially HHV-6/7, EBV, and CMV), introduction of new drugs, or rapid tapering of therapeutic systemic corticosteroids.

Although pathogenesis is not exactly known, DRESS is primarily regarded a delayed type IVb immune response to a drug, possessing an innate ability to stimulate T-cells, in which eosinophils are prominent and CD8+ cytotoxic T-cells are important effector cells. Moreover, a complex interplay involving herpes virus related factors, immunological mechanisms, drug detoxification pathways, and a genetic predisposition are presumed. Although associated with many drugs, the number of implicated “high risk” drugs seems rather limited with aromatic anticonvulsants, allopurinol and sulfonamides as most notorious (Table 2).

TABLE 1

RegiSCAR DRESS validation score						
SCORE	**-1**	**0**	**1**	**2**	**min**	**max**
Fever ≥ 38.5°C	No/U	Yes			-1	0
Enlarged lymph nodes		No/U	Yes		0	1
Eosinophilia		No/U			0	2
Eosinophils			700-1499/µl	≥1500/µl		
Eosinophils, if leukocytes <4000			10-19.9%	≥20%		
Atypical lymphocytes		No/U	Yes		0	1
Skin involvement					-2	2
Rash extent (> 50% BSA)		No/U	Yes			
Rash suggesting DRESS	No	U	Yes			
Biopsy suggesting DRESS	No	Yes/U				
Organ involvement *					0	2
Liver		No/U	Yes			
Kidney		No/U	Yes			
Lung		No/U	Yes			
Muscle/heart		No/U	Yes			
Pancreas		No/U	Yes			
Other organ(s)		No/U	Yes			
Resolution ≥ 15 days	No/U	Yes			-1	0
Evaluation other potential causes:					0	1
ANA						
Blood culture						
Serology for HVA/ HVB/ HVC Chlamydia-/ Mycoplasma pneumoniae						
Other serology/PCR						
If none positive and ≥ 3 of above negative			Yes			
TOTAL SCORE					-4	9

Criteria and limits for scoring the signs and symptoms are disseminated in the online material of Reference 1.

U = unknown/unclassifiable

** After exclusion of other explanations: 1 = 1 organ, 2 = ≥ 2 organs; Final score <2: No case; Final score 2-3: Possible case; Final score 4-5: Probable case; Final score >5: Definite case*

The number of drug–HLA associations with a raised risk in various ethnic groups and populations is expanding (Table 3). Genetic screening, already recommended in Taiwan for B*58:01 before prescribing allopurinol, will improve drug safety for at-risk patients.

In vivo and *in vitro* testing with the suspected drug(s) is helpful to confirm diagnosis and assign the culprit, but should only be performed 6 weeks to 3 months after resolution of DRESS; sensitivity and specificity are variable, also depending on the drug involved. Positive patch reactions in DRESS have been described in 32.1%, most often for anti-epileptics, especially carbamazepine, while one multicenter study reported 64%. Rechallenge with the culprit, even a small test dose, may result in a quick recurrence and even near-fatal reactions and should not be performed.

Early recognition and prompt withdrawal of the culprit drug is the most decisive step to avoid progression. Treatment further includes supportive care, antihistamines, and/or potent topical corticosteroids. For severe cases with serious organ involvement, systemic corticosteroids are advised. Introduction of new drugs should be avoided because of the risk of flare up, sensitization and "multiple drug allergy".

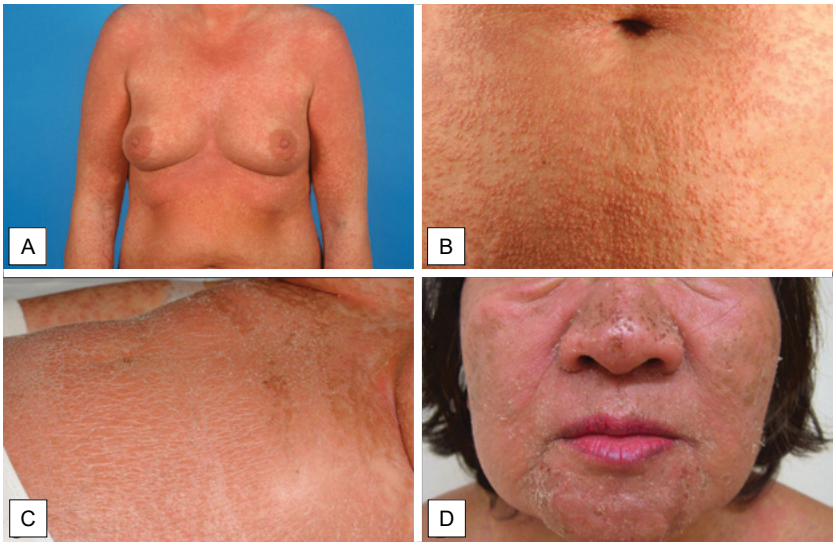

Figure 1 Clinical manifestations of DRESS. A. Extensive erythematous maculopapular rash with infiltrated papules. B. Close-up of infiltrated papules on the abdomen. C. Exfoliative dermatitis. D. Facial and peri-orbital oedema, scaling, and residual facial erythema and pustules

TABLE 2

Highly notorious drugs in DRESS	
Allopurinol	**Sulfonamides**
	Dapsone
Antiepileptic drugs	Sulfadiazine
Carbamazepine	Sulfasalazine
Lamotrigine	**Antibiotics**
Oxcarbazepine	Minocycline
Phenytoin	Vancomycin
Primidone	**Fluindione**
Zonisamide	**Mexiletine**
	Nevirapine
	Strontium ranelate

TABLE 3

Major known drug-HLA/CYP associations in DRESS		
Associated drug	**HLA allele / metabolic enzyme**	**Ethnicity / population**
Carbamazepine	A*31:01	Han Chinese, Japanese, Korean, European, Spanish
Phenytoin	A*24:02 B*51:01 B*15:13 CYP2C9*3	Spanish Thai Malaysian Han Chinese, Malaysian
Lamotrigine	A*24:02	Spanish
Allopurinol	B*58:01	Han Chinese, Korean, Japanese, Thai, European
Nevirapine	B*14:02/ Cw*8 Cw*8 C*04:01	Italian Japanese Malawian
Dapsone	B*13:01	Han Chinese

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5f CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS (SJS/TEN)

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KEY MESSAGES

- SJS and TEN are a single disease entity of different severity but with common causes and mecha-nisms. They are either referred to as SJS/TEN or EN for "epidermal" or "epithelial necrolysis"
- Diagnostic means include a biopsy, sometimes also immunofluorescence test and thorough assess-ment of clinical features as well as a detailed medication and infection history
- Approx. 75% of SJS/TEN-cases are drug-induced, but only 50% in children. Non-drug cases are viral infections, e.g. flu-like illness, respiratory infections, esp. in children and young adults, but also un-known inducers leading to the denomination of "idiopathic cases"
- "High risk" drugs for SJS/TEN are allopurinol, antiinfective sulfonamides, certain anti-epileptic drugs, nevirapine and oxicam-NSAIDs, which account for more than half of the cases
- Treatment requires a multiprofessional, interdisciplinary team with high standards of supportive care. Immunomodulation therapy may be helpful in the early stage of SJS/TEN, as long as skin detach-ment is still progressing. Among various immunomodulating agents, cyclosporine A has shown the most favourable results

CLINICAL PICTURE

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute life-threatening conditions characterized by erythematous skin and extensive detachment of epidermis as well as hemorrhagic erosions of mucous membranes (Figure 1). They are considered as a single dis-ease entity of different severity but with common causes and mechanisms. Thus, they are either re-ferred to as SJS/TEN or EN for "epidermal" or "epithelial necrolysis". The differentiation is based on the extent of skin detachment, which is determined once the progression of skin detachment has stopped. When this is limited to less than 10% of the body surface area (BSA), the condition is called SJS, when it is widespread with more than 30% of the BSA it is named TEN and in-between defined as SJS/TEN-overlap (Table 1). Nikolsky-sign is positive revealing a "wet" ground when the necrotic epidermis is slightly pushed away. The histopathology reveals subepidermal separation and necrotic keratinocytes either in wide dissemination or full-thickness necrosis of the epidermis induced by extensive apoptosis. The disease typically starts with unspecific symptoms, such as fe-ver, malaise, headache, oronasal soreness, sand-like feeling of the eyes, which precede the objective signs of erythematous skin or mucosa by one to three days. Vesicles or blisters follow sometimes rapidly within one day, sometimes with delay (Figure 2).

DIFFERENTIAL DIAGNOSIS

Most differential diagnoses can be distinguished through histopathology and/or immunofluorescence test, e.g. staphylococcal scalded skin syndrome (SSSS), bullous autoimmune diseases, subacute cu-taneous lupus erythematosus. Some conditions showing the same histological pattern have to be sep-arated by clinical features, such as erythema (exsudativum) multiforme (E(E)M)

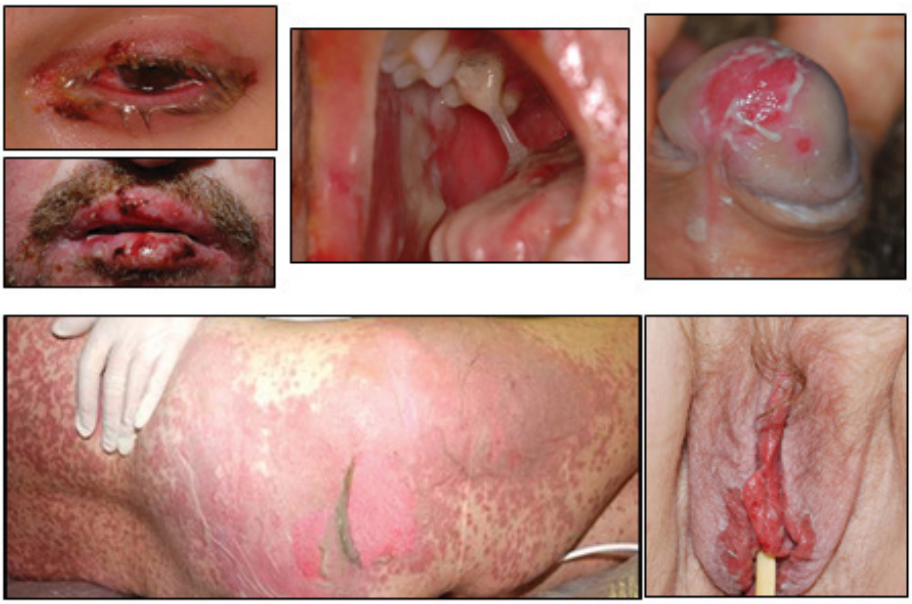

Figure 1 Clinical pattern of SJS/TEN with skin blisters and mucosal erosions

TABLE 1

Modified Consensus definition of SJS/TEN [1, 4]					
Criteria	**Typical EMM**	**Atypical EMM**	**SJS**	**SJS/TEN overlap**	**TEN with maculae**
Skin detachment (%)	2-3%	<10%	<10%	10-30%	>30%
Typical target lesions	+	+	-	-	-
Atypical target lesions	raised	raised, large	flat	flat	flat
Maculae	-	-	+	+	+
Distribution	mainly limbs	widespread	widespread	widespread	widespread

EMM= erythema multiforme majus, SJS = Stevens-Johnson syndrome, TEN= toxic epidermal necrolysis

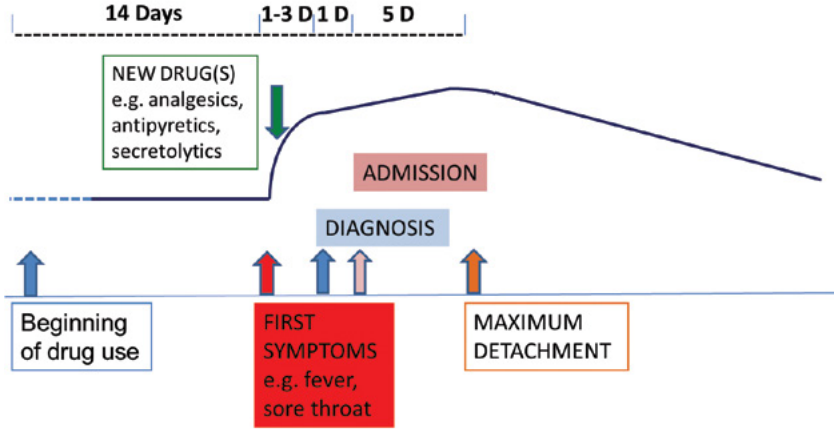

Figure 2 Course of SJS/TEN

TABLE 2

Drugs and recommendations in SJS/TEN [2, 6]
A. Drugs with a high risk to induce SJS/TEN
Their use should be carefully evaluated and they should be suspected promptly.
Allopurinol
Carbamazepine
Co-trimoxazole (and other anti-infective sulfonamides and sulfasalazine)
Lamotrigine
Nevirapine
NSAIDs (oxicam type, e.g. meloxicam)
Phenobarbital
Phenytoin
An interval of 4-28 days between beginning of drug use and onset of the adverse reaction is most suggestive of an association between the medication and SJS/TEN.
When patients are exposed to several medications with high expected benefits, the timing of administration is important to determine which one(s) must be stopped and if some may be continued or re-introduced.
The risks of various antibiotics to induce SJS/TEN are within the same order of magnitude, but substantially lower than the risk of anti-infective sulfonamides.
B. Drugs with a moderate (significant but substantially lower) risk for SJS/TEN
Cephalosporines
Macrolides
Quinolones
Tetracyclines
NSAIDs (acetic acid type, e.g. diclofenac)
C. Drugs with no increased risk for SJS/TEN
Beta-blockers
ACE-inhibitors
Calcium channel blockers
Thiazide diuretics (with sulfonamide structure)
Sulfonylurea anti-diabetics (with sulfonamide structure)
Insulin
NSAIDs (propionic acid type, e.g. ibuprofen)
Valproic acid

and generalized bullous fixed drug eruption (GBFDE).

For decades EM with mucosal involvement (EM majus, EMM) was considered as SJS leading to false assessment of prognosis and etiology, which in EMM are predominantly infections and not medications. The consensus definition differentiating both entities has been refined demonstrating that target lesions tend to occur in acral distribution in adults, but in widespread distribution in children, which may partly explain the misclassification. GBFDE usually presents with well-defined round or oval patches of dusky violaceous or brownish colour. Blisters develop on these patches, but typically skin detachment is limited. However, the reaction may also appear as dif-fuse erythema with blisters showing demarcation during the course. Nikolsky-sign is positive on the areas with marked erythema but not beyond. Fever and mucosal involvement occur rarely, but peri-orificial erosions are common. The history frequently reveals previous eruptions.

EPIDEMIOLOGY

With an incidence of 1-2 cases per one million persons per year SJS/TEN are rare, but may affect persons of various ethnicities and age groups, being more common in elderly than in children or young adults. In a population-based study in Germany, the average age of patients with validated SJS/TEN was 53.4 years (1-94 years) for more than 2200 patients. The mortality rate was 9% for SJS, 29% for SJS/TEN-overlap and 48% for TEN, altogether almost 25% for the entire cohort. Risk factors for death in the acute stage of the disease are large amount of skin detachment, old age and renal failure, whereas death in the first year after SJS/TEN is related to pre-existing conditions such as hepatic insufficiency and active malignant disease.

ETIOLOGY

Most cases of SJS/TEN are caused by drugs (75%), unless in children, where in only 50% a drug cause may be identified. Half of the pediatric cases have non-drug causes, esp. flu-like illness and viral respiratory infections. Drugs with a high risk to induce SJS/TEN are listed inTable 2. The culprit drug is typically taken for the first

time in consecutive use of one to four weeks. Medica-tions taken for many years or very shortly before the reaction and those used and well tolerated be-fore are very unlikely causes of SJS/TEN. Furthermore, medications to treat the prodromal symptoms like antipyretics, analgesics or secretolytics should not be considered to be causal. The algo-rithm for assessment of drug causality in EN (ALDEN) provides structured help to identify the most likely culprit drug. For confirmation of the inducing drug, in-vitro or in-vivo tests typically used in allergologic work-up are not reliable in SJS/TEN, and oral provocation test cannot be recommend-ed for safety reasons.

THERAPY

Withdrawal of the most likely culprit drug in drug-related casesis crucial. The severity of illness score (SCORTEN) allows for a prognostic assessment of the patient. The higher the score, the poorer the prognosis and the more likely the need for intensive care. Supportive care includes elevation of room temperature, bedding on air-fluidized beds, pain control or sedation, aseptic skin care, fluid replacement, nutrition through a gastric tube, if oral mucosa is affected or intubation is needed, pre-vention of adhesions, if genital mucosa is involved, etc. Prophylactic antibiotic use is not recom-mended, but rather close monitoring for infection of any kind and appropriate antibiotic treatment if necessary. All patients should be examined by an experienced ophthalmologist. If there is eye-involvement, ophthalmologic consultation is needed at least every other day. In terms of im-munomodulating treatment, several studies in different centers have demonstrated a benefit for cy-closporine A when applied in the early phase of the disease. Also steroids had a positive effect quoad vitam, when administered in a medium dose for only a couple of days, whereas for intrave-nous immunoglobulins (IVIG) no significant positive effect could be demonstrated. Few not convincing data are available concerning treatment with anti-tumor necrosis factor (TNF)-alpha like etanercept.

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5g CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: FIXED DRUG ERUPTION INCLUDING GENERALIZED BULLOUS FIXED DRUG ERUPTION (GBFDE)

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KEY MESSAGES

- FDE may often present with atypical features that mimic other skin diseases, such as erythema multiforme and parapsoriasis en plaques
- Patients with generalised bullous FDE can be misdiagnosed as Stevens-Johnson syndrome (SJS). After drug discontinuation, most FDE lesions resolve without treatment in a few days, unlike SJS
- Localized epidermal injury that characterises fixed drug eruption (FDE) is mediated by intraepidermal CD8+T cells with the resident-memory phenotype

Fixed drug eruption (FDE) is a cutaneous drug reaction characterised by a recurrent onset of a solitary or a small number of well-circumscribed, round, and/or oval erythematous macules and plaques in the same sites with each administration of the causative drug.

The most common locations are the lip, palms, soles, glans, penis and groin. Drugs causing FDE differ in countries depending on the availability; the most frequently associated drugs are pseudoephedrine, trimethoprim, tetracycline and barbiturates. The lesions usually flare within 30 min to 8h after drug intake (Figure 1). FDE lesions become more numerous and more severe unless the causative drug is withdrawn. FDE lesions can also be reproduced upon administration of related drugs/agents with chemical structures similar to the inducing drug (cross-reactivity).

FDE often presents with a wide spectrum of clinical manifestations indistinguishable from those of other skin disease: they include erythema multiforme, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), bullous pemphigoid, lichen planus and parapsoriasis en plaques. Such unusual variants may be easily overlooked unless clinicians take special care to recognize the presence of such variants. As blister formation often occurs at an advanced stage of FDE in association with systemic symptoms, clinicians may find a great deal of difficulty in distinguishing between a multiple, bullous variant of FDE (generalised bullous FDE) (Figure 2) and SJS/TEN. Careful history-taking about drug intake and a prior history of recurrent lesions in the same sites are essential for the diagnosis of FDE. The diagnosis can be made on the basis of prompt resolution upon withdrawal of the causative drug and the reproducibility of the eruption by administration of the drug. Systemic oral challenge tests are usually performed to identify the drug responsible for the FDE with relative safe. In most cases, patch tests should be performed with the drug mixed in petrolatum to 10~20% (Figure 3).

Intraepidermal CD8+T cells with the resident-memory phenotype ($CD8+T_{RM}$) resident in the FDE lesions are crucial in the initiation of localized epidermal damage. Indeed, resting FDE lesions long after clinical resolution are characterized by significant numbers of $CD8+T_{RM}$ aligning along the epidermal side of the dermoepidermal junction (Figure 4). Localised tissue damage results when $CD8+T_{RM}$ are activated to direct-

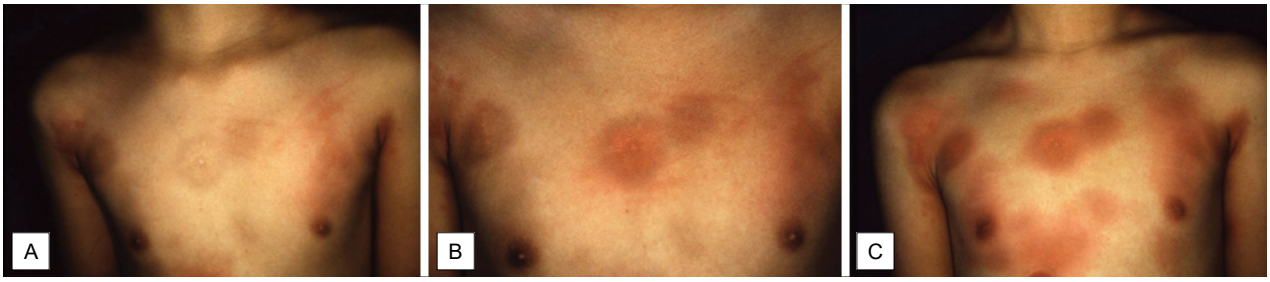

Figure 1 Clinical manifestations of multiple FDE lesions 20 min (A), 1h (B) and 4h (C) after clinical challenge with the causative drug

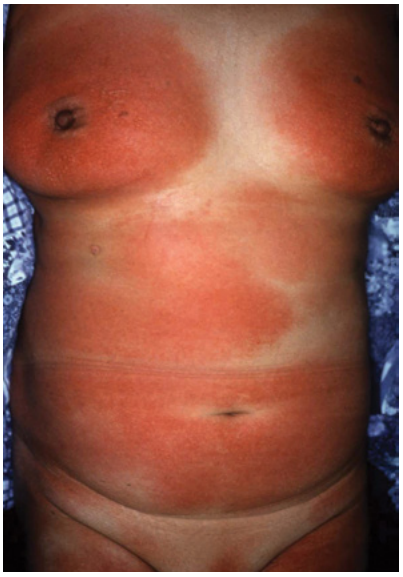

Figure 2 Typical presentation of generalized bullous FDE simulating severe drug eruption. Characteristic well-circumscribed, round erythematous plaques, partly coalescing

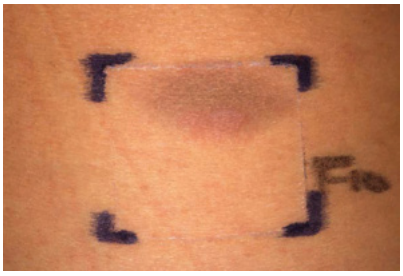

Figure 3 Positive patch test reactions confined to the previously involved pigmented skin

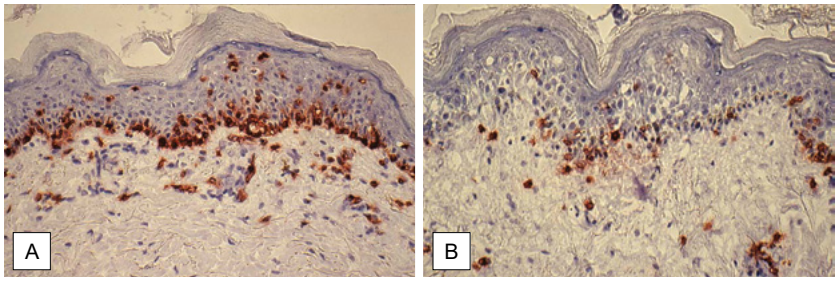

Figure 4 $CD8^+$ resident-memory T-cells reside only in the lesional skin before (A), but not 24 hours after (B) clinical challenge

ly kill surrounding keratinocytes and release large amounts of cytokines such as IFN-γ into the local microenvironment. Regulatory T cells recruited during the active stage could serve to limit excessive activation of $CD8+T_{RM}$, resulting in spontaneous resolution upon withdrawal of the causative drug.

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5h

CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: LOCAL DRUG REACTIONS/ INJECTION-SITE REACTIONS

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KEY MESSAGES

- Injection-site reactions are mainly local reactions that rarely disseminate
- Injection-site reactions can be triggered by various drugs administered intramuscularly or subcutaneously
- Most injection-site reactions are mild and self-limiting

Reactions in the skin after local administration of drugs may occur, in particular for drugs administered subcutaneously or intramuscularly such as vaccines, insulins, allergen immunotherapy and biologicals (biologicals described below in the following section).

The majority of the injection-site reactions are non-immediate commencing several hours or days after injection (Figure 1). The symptoms are swelling, erythema, pruritus and pain persisting for hours to a few days. The clinical picture is an erythematous plaque. Rarely, it may present with bullae, ulcerations or necrosis. On rare occasions a delayed injection-site reaction can develop into a systemic maculopapular rash. It may occur if treatment with the culprit drug is not discontinued. Sometimes the injection-site reactions occur immediately after injection presenting as a wheal indicating a type I reaction.

Vaccines administered to both children, adolescent, or adults often cause a non-immediate local injection-site reaction which is a common adverse effect that does not contraindicate future dosing.

The majority of patients undergoing subcutaneous allergen immunotherapy (with aeroallergens or hymenoptera allergens) will experience local injection-site reactions that may develop immediately or several hours after injection and persist for days. If a large reaction appears after injection, it may be relevant to administer the same or a lower dose at subsequent injection in order to prevent a systemic allergic reaction.

Reactions caused by insulin injections are very rare and may be a type I allergy presenting with wheals developing around the injection-site(s) and occasionally it develops into generalized urticaria and/or other symptoms of anaphylaxis. More commonly delayed reactions surrounding the injection-site will occur. Patients with suspected reactions to insulin should be referred to a specialist centre for testing. The patient may benefit from insulin desensitization if treatment with oral antidiabetics is not an option.

Other constituents of the vaccine/drug can trigger a reaction, e.g. aluminum used as adjuvant in vaccines. Often it does not cause a large edematous swelling but rather redness and/or a subcutaneous invisible but palpable nodule (granuloma).

Differential diagnoses to injections-site reactions are fixed drug eruptions or a photoallergic reaction. However, the case history of injection of a drug will often provide the diagnosis.

If generalized symptoms occur (anaphylaxis, maculopapular rash, or other systemic symptoms) in relation to the local reaction, the patient should be referred to a specialist centre for evaluation.

Bothersome symptoms can be alleviated with cold packs, antihistamines or topical steroids.

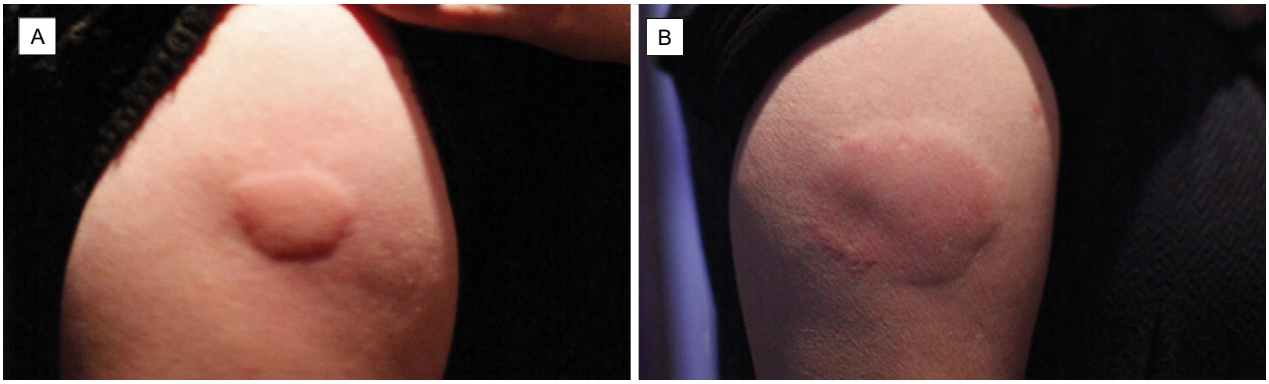

Figure 1 Immediate reaction (A) 30 minutes after injection and delayed reaction 24 hours (B) after injection in a patient undergoing allergen immunotherapy.

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5i

CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: SPECIAL SKIN REACTIONS TO CHEMOTHERAPEUTIC DRUGS

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KEY MESSAGES

- Skin toxicity is a frequent, sometimes severe, adverse effect provoked by "traditional chemotherapy"
- It's possible to divide skin reactions into 8 main types, underlying different patho-mechanisms
- Hypersensitivity reactions (HSRs) to chemotherapeutic drugs have been documented for most cancer chemotherapies and involve the skin in many cases
- Chemotherapy causes a group of overlapping toxic reactions, defined toxic erythema, that are characterized by areas of painful erythema (and often edema) which usually involve the hands and feet, intertriginous zones (eg, axillae, groin), and, less often, the elbows, knees, and ears

"Traditional" chemotherapy causes various cutaneous manifestations with underlying different patho-mechanisms. It is possible to divide the skin reactions in the following main types:

- Hypersensitivity reactions
- Toxic erythema
- Alopecia
- Extravasation
- Photosensitivity
- Pigmentary disorders
- Nail changes
- Severe cutaneous adverse reactions (Steven-Johnson Syndrome, toxic epidermal necrolysis)

Hypersensitivity reactions (HSRs) to chemotherapeutic drugs have been documented for most cancer chemotherapies and in many cases involve the skin. The classification by Coombs and Gell divides drug reactions into four immunologically distinct types which may be associated with specific skin changes (Table 1). However, HSRs reactions to chemotherapy that involve the skin could be also triggered by preservatives, co-solvents or other additives with non-immune-mediated mechanisms.

Between chemotherapeutic drugs, most skin reactions are caused by platinum compounds taxanes and asparaginase.

TOXIC ERYTHEMA

While some of the drug reactions are allergic in nature, there is a group of overlapping toxic reactions- defined toxic erythema- that is characterised by areas of painful erythema (and often edema) which usually involve the hands and feet, intertriginous zones (eg, axillae, groin), and, less often, the elbows, knees, and ears. The eruptions may have a bullous component, are self-limited, and often resolve with desquamation and post-inflammatory hyperpigmentation (Table 2). Toxic erythema of chemotherapy can be provoked by several chemotherapeutics, namely, anthracyclines antimetabolites, mitotic inhibitors, vinca alkaloids.

The most common and well-studied entity is hand-foot syndrome (HFS) (Figure 1).

In regard to the therapy, currently the most effective management of HFS is treatment interruption or dose-intensity modification with symptoms improving in 1-2 weeks. Symptom-control includes the use of high-potency steroids, wound care to prevent infections, and topical keratolytics to decrease hyperkeratosis.

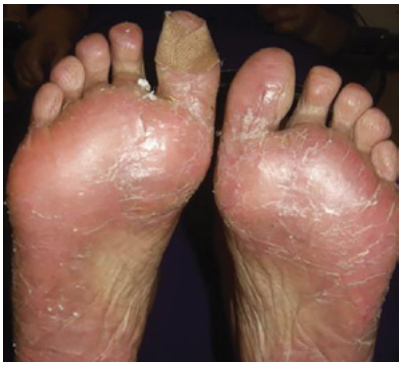

Figure 1 Hand-Foot Syndrome by capecitabine

OTHER SKIN REACTIONS ASSOCIATED WITH CONVENTIONAL CHEMOTHERAPY

Chemotherapeutic drugs can provoke, with variable frequency, other muco-cutaneous side effects represented by extravasation, photosensitivity, pigmentary disorders, nail changes, and alopecia. All these reactions are bothersome but alopecia greatly impairs quality of life, especially for women. Although typically reversible, chemotherapy-induced alopecia (CIA) is a physical and psychological sequelae that can negatively impact patient perceptions of their appearance, body image, sexuality, and self-esteem (Figure 2). The majority of chemotherapeutics can induce alopecia, but this side effect is more common with anthracyclines, taxanes and topoisomerase inhibitors (60-100%). Scalp hypothermia, or scalp cooling (SC), during chemotherapy administration, prevented alopecia in 50–80% of patients and a recent meta-analysis concluded that scalp hypothermia was the only intervention that significantly reduced the risk of CIA.

TABLE 1

Allergic reactions of the skin due to cytostatic agents

Reaction type	Skin manifestation	Culprit agents
I IgE-mediated	Urticaria Angioedema Exanthem Pruritus	Asparaginase Azathioprine Cyclophosphamide Chlorambucil Platinum compounds Daunorubicin Docetaxel Doxorubicin Etoposide Gemcitabine Mechlorethamine Melphalan Methotrexate Paclitaxel Thiotepa
II Cytolytic antibodies (IgG or IgM)	Bulllous eruptions Urticaria Purpura	Cytarabine
III Antigen-antibody immune complex	Urticaria Vasculitis Exanthems	Asparaginase Azathioprine Bendamustine Busulfan Chlorambucil Cisplatin Cyclophosphamide Hydroxyurea Procarbazine Thiotepa
IV Cell-mediated sensitized T lymphocytes	Contact dermatitis Pseudolymphoma	Bendamustine BCNU Cytarabine Daunorubicin Doxorubicin 5-fluorouracil Mitomycin C

TABLE 2

Entities within the spectrum of toxic erythema of chemotherapy	
Ara C (cytarabine) ears	Palmar-plantar (palmoplantar) erythrodysesthesia
Burgdorf's reaction	Toxic acral erythema
Chemotherapy-associated eccrine reactions	Toxic erythema of the palms and soles
Eccrine squamous syringometaplasia, chemotherapy-induced	Intertriginous eruption associated with chemotherapy
Epidermal dysmaturation, chemotherapy-induced	Intertrigo-like eruption, chemotherapy-induced
Epidermal dystrophy (secondary to cytotoxic agents*)	Flexural erythematous eruption (following autologous
Erythrodysesthesia	PBSCT)
Acral erythema	Intertrigo dermatitis
Acral erythrodysesthesia	Neutrophilic eccrine hidradenitis, chemotherapy-associated
Chemotherapy-induced acral erythema (CIAE or CAE)	Chemotherapy-induced hidradenitis
Hand- foot syndrome	Drug-induced hidradenitis
Palmar-plantar erythema	

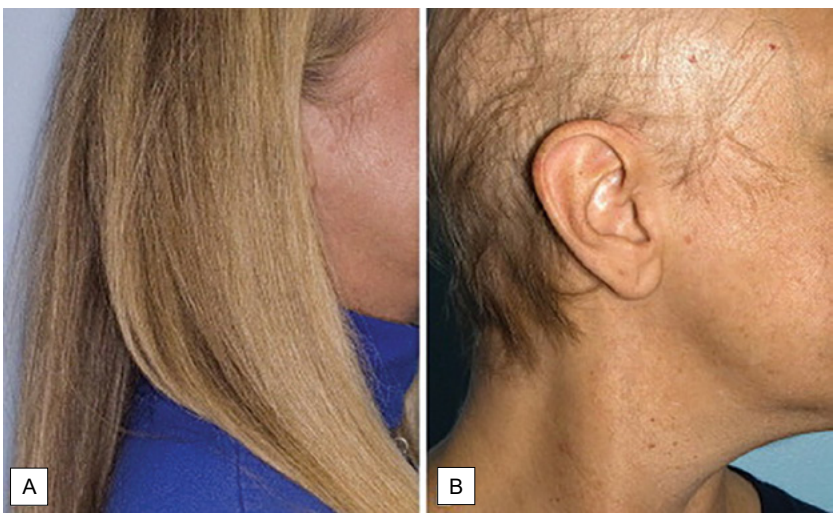

Figure 2 Alopecia provoked by epirubicin

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5j

CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: SPECIAL SKIN REACTIONS TO BIOLOGICALS

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KEY MESSAGES

- Biological therapies demonstrate a wide variety of cutaneous adverse reactions ranging from local injection site reactions to serious hypersensitivity
- TNF-a inhibitors, IL-12/23 inhibitors and IL-6 inhibitors can cause psoriasis flares or lead to the manifestation of psoriasis
- IL-17 inhibitors increase the risk for Candida infections
- IL-4/13 inhibitors are associated with increased rates of conjunctivitis

Biologic agents are genetically-engineered proteins designed to reduce inflammation by inhibiting special components of the immune system. These include fusion proteins and targeted monoclonal antibodies against interferons, recombinant interleukins, growth factors, enzymes, which have been widely used in the past two decades in the treatment of various diseases. Their tolerability and safety profile are satisfactory; however, an increasing number of side effects have been reported. Cutaneous adverse reactions are among the most frequently observed toxicities and may even lead to discontinuation of these therapies. Some of the most commonly used biological therapies and their reported cutaneous adverse events are listed in Table 1.

TNF INHIBITORS (TUMOR NECROSIS FACTOR INHIBITORS)

Rheumatological studies have shown that 25% of patients undergoing anti-TNF therapy will develop some kind of skin reaction. Other than infusion/injection site reactions, psoriasis and psoriasis-like lesions, lupus-like syndromes, cutaneous vasculitis, and cutaneous infections (bacterial cellulitis, erysipelas, absesses, HSV, VZV, CMV, HPV, Candida species) have the strongest association with anti-TNF treatments. These are followed by eczematous reactions, lichenoid and granulomatous reactions. Non melanoma skin cancers, especially squamous cell carcinomas have also been observed, however rather rarely.

IL-17 INHIBITORS

IL-17 inhibitors represent the newest biological therapies for treatment of moderate to severe plaque psoriasis, therefore their complete spectrum of cutaneous adverse events remains to be seen. Injection site reactions were reported as the third most frequent side effect (nasopharyngitis and upper respiratory tract infections in the first two places). An increased Candida species skin and mucosal infection rate are also frequent in patients under IL-17 treatment.

IL-12/23 INHIBITORS

Injection site reactions have been reported for ustekinumab and guselkumab, however in at similar or slightly elevated rates than placebo. Paradoxical worsening or manifestation of psoriatic plaques and psoriatic arthritis have been described under ustekinumab therapy. Patients treated with guselkumab are at higher risk for herpes simplex and tinea infections.

IL-1 INHIBITORS

Local injection site reactions are by far the most frequent cutane-

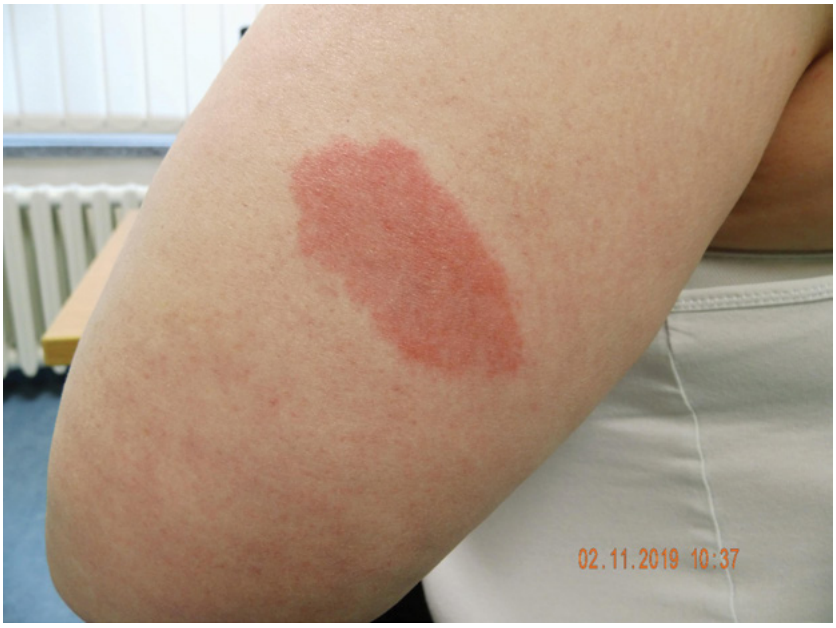

Figure 1a Injection site reaction at the upper left arm after anti-IL 4/13 (Dupilumab) s.c. injection

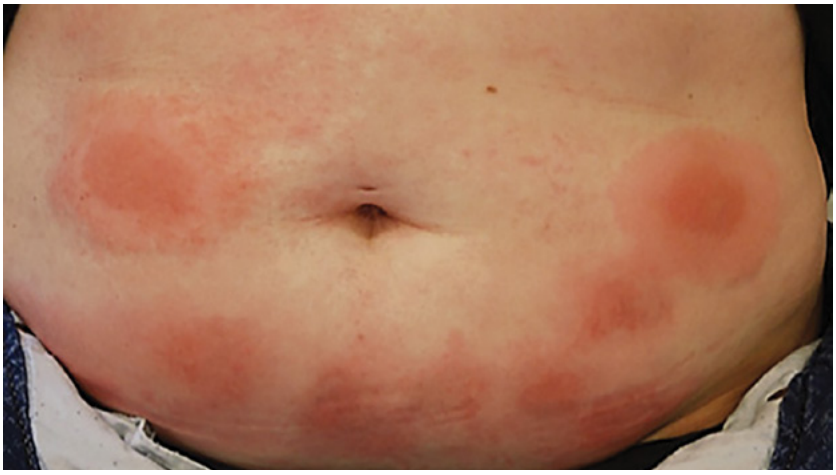

Figure 1b Multiloculated abdominal injection site reactions after anti-IL-1 (Anakinra) s.c. treatment

ous side effect of IL-1 inhibitors. Most of these reactions are mild, occur in the first month of treatment, and show resolution within approximately a week (Figure 1b). Non-specific drug eruptions have also been described; DRESS syndrome has been recently described in two cases and is extremely rare under IL-1 treatment.

CONCLUSIONS

Skin reactions to biological therapies show a great diversity, varying from mild local injection reactions to systemic hypersensitivity reactions that oblige the discontinuation of the therapy. TNF inhibitors and IL-12/23 can paradoxically, although indicated for the treatment of psoriasis, result in psoriasis flares and IL-17 inhibitors increase the risk of Candida infections. IL-4/13 inhibitors are associated with the occurrence of conjunctivitis and IL-1 inhibitors with prominent local injection reactions. It is crucial for clinicians to be aware of the possible cutaneous side effects of biologics and treat accordingly or in rare cases proceed to the discontinuation of the implicated biological therapy.

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TABLE 1

Selection of commonly used biological therapies, their mechanism of action, indications and reported adverse cutaneous manifestations. Marked in bold the most frequently observed in each drug class *

Drug target	Active agent	Mechanism of action	Indication	Selection of reported cutaneous adverse reactions
TNF inhibitors	Infliximab (Remicade®)	Forms a durable complex with TNFa, thus leading to TNF loss of activity	Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis, Crohn disease, Ulcerative colitis, Ankylosing spondylitis	**Skin infections** (bacterial, fungal, viral), **eczema**, actinic keratosis, non-melanoma skin cancer (especially squamous cell carcinomas), **infusion reactions to i.v. Infliximab, injection site reactions, lupus/lupus-like lesions**, cutaneous vasculitis, erythema nodosum, purpuric rash, bullous pemphigoid, linear IgA bullous dermatitis, erythema multiforme-like reactions, eosinophilic cellulitis (Wells' syndrome), Sweet syndrome, eczematous dermatitis, **paradoxical psoriasis onset or worsening**, urticarial reaction, lichenoid eruption, Alopecia areata, folliculitis, palmoplantar psoriasis, psoriasis pustulosa, interface dermatitis, Morphea, eruptive growth of benign lesions (seborrheic keratosis, ruby angiomas, fibropapillomas), leukocytoclastic vasculitis, folliculitis-like lichenoid sarcoidosis, cutaneous focal mucinosis
	Etanercept (Enbrel®)	Inhibits TNFa and TNFβ binding to cell surface TNF receptors	Rheumatoid arthritis, Plaque psoriasis, Psoriatic arthritis, Ankylosing spondylitis, Juvenile idiopathic arthritis	
	Adalimumab (Humira®)	Inhibits TNFa specifically and blocks its binding with cell surface TNF receptors	Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Plaque psoriasis, Crohn disease, Ulcerative colitis, Hidradenitis suppurativa, Uveitis, Juvenile idiopathic arthritis	
	Certolizumab pegol (Cimzia®)	Binds and neutralizes both soluble and transmembrane TNFa	Crohn disease, Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Plaque psoriasis	
	Golimumab (Simponi®)	Forms stable complexes with TNFa, thus blocking TNFa receptor binding	Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Ulcerative colitis	
IL-12/23 inhibitors	Ustekinumab (Stelara®)	Binds to p40 protein shared by IL-12 and IL-23	Plaque psoriasis, Psoriatic arthritis, Crohn disease	Injection site reactions, paradoxical psoriasis onset or worsening/ psoriatic arthritis flares, urticaria, Alopecia areata, linear IgA bullous dermatosis, eczematous drug reaction, lymphomatoid drug reaction, erythema annulare centrifugum
	Guselkumab (Tremfya®)	Selectively binds to the p19 subunit of IL-23 in dendritic cells and keratinocytes and blocks its interaction with IL-23 receptor	Plaque psoriasis	**Injection site reactions**, herpes simplex infections, tinea infections
IL-17 inhibitors	Secukinumab (Cosentyx®)	Binds IL-17a and prevents its binding to the receptor	Plaque psoriasis, Psoriatic arthritis, Ankylosing spondylitis	**Injection site reactions**, urticaria, **mucocutaneous candidiasis**, exacerbation of oral herpes, oral lichenoid reaction
	Ixekizumab (Taltz®)	Binds IL-17a and prevents its binding to the receptor	Plaque psoriasis, Psoriatic arthritis	
	Brodalumab (Kyntheum®)	Binds IL-17a receptor and prevents binding of IL-17a to the receptor	Plaque psoriasis	

Drug target	Active agent	Mechanism of action	Indication	Selection of reported cutaneous adverse reactions
IL-1 inhibitors	Anakinra (Kineret®)	Competitively inhibits IL-1 binding to the IL-1 type I receptor	Rheumatoid arthritis, Cryopirin-associated periodic syndromes (CAPS), Systemic juvenile idiopathic arthritis (SJIA), Adult onset Still's disease (AOSD)	**Injection site reactions**, non-specific rash, drug reaction with eosinophilia and systemic symptoms (DRESS)
	Rilonacept (Arcalyst®)	Binds IL-1β, thus blocking its binding to cell surface receptors; also binds IL-1α and IL-1 receptor antagonist with lower affinity	CAPS	
	Canakinumab (Ilaris®)	Binds IL-1β, thus blocking ist binding to cell surface receptors	CAPS, Tumor Necrosis Factor (TNF) receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF)	
IL-6 inhibitors	Tocilizumab (Acterma®, RoActemra®)	Binds soluble and membrane-bound IL-6 receptors	Rheumatoid arthritis, Giant cell arteritis, Cytokine release syndrome, Systemic juvenile idiopathic arthritis	**Injection site reactions**, hypersensitivity drug reactions, cellulitis, urticaria, Stevens-Johnson syndrome, herpes simplex infection, psoriasiform rash, cutaneous vasculitis, skin ulceration
	Siltuximab (Sylvant®)	Binds to IL-6, thus preventing binding to soluble and membrane bound receptors	Castleman disease	
IL-4/13 inhibitors	Dupilumab (Dupixent®)	Binds to the alpha subunit of the interleukin-4 receptor (IL-4Rα). Through blockade of IL-4Rα, dupilumab modulates signaling of both the interleukin 4 and interleukin 13 pathway	Atopic dermatitis	**Injection site reactions, conjunctivitis**, herpes simplex virus infections, non-specific rash
IL-5 inhibitors	Mepolizumab (Nucala®)	Binds to IL-5 and therefore stops IL-5 from binding to its receptor on the surface of eosinophils	Asthma, Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)	**Injection site reactions**, non-specific skin rash
	Reslizumab (Cinqair®)	Binds to human IL-5 to inhibit IL-5 signaling and prevents the binding of IL-5 to the IL-5 receptors	Eosinophilic asthma	

Drug target	Active agent	Mechanism of action	Indication	Selection of reported cutaneous adverse reactions
B-Cell depletion	Rituximab (Rituxan®)	Binds CD20 and mediates B-cell lysis	Non-Hodgkin lymphoma, Chronic lymphocytic leukemia, Rheumatoid arthritis, Wegener granulomatosis, Microscopic polyangiitis, Pemphigus vulgaris	Drug-induced urticarial dermatitis, maculopapular rash, aphthous ulcers/mucositis, Stevens-Johnson syndrome, cutaneous vasculitis, infusion reactions (i.v. administration), delayed serum sickness, injection site reaction (s.c. administration), Sweet syndrome, skin infections, folliculitis, temporary mild hair loss
	Belimumab (Benlysta®)	Binds B-lymphocyte stimulator (BLyS) and prevents BLyS from binding B cells, thus reducing B Cell survival	Systemic lupus erythematosus	
JAK-3 inhibitor	Tofacitinib (Xeljanz®)	Inhibits Janus Kinase JAK3, a group of intracellular enzymes involved in signaling pathways that affect hematopoiesis and immune cell function	Rheumatoid arthritis, Psoriatic arthritis, Ulcerative colitis	Herpes zoster infection, acne
Kalikrein Inhibitor	Lanadelumab (Takhzyro®)	Inhibits plasma kalikrein, thus preventin cleavage of kininogen to bradykinin	Hereditary angioedema types 1 & 2	Maculo-papular rash, **injection site reactions**
IgE inhibitor	Omalizumab (Xolair®)	Inhibits the binding of IgE to receptors on mast cells and basophils	Asthma, chronic spontaneous urticaria	Injection site reactions (rare)
EGFR inhibitor	Cetuximab (Erbitux®)	Binds specifically to the extracellular domain of EGFR as a competitive antagonist of the endogenous ligands, thus leading to downregulation of EGFR on the cell surface	Colorectal cancer, Head and neck cancer	**Skin toxicity** including papulo-pustular eruption, acneiform dermatitis, skin xerosis, asteatotic eczema, fissures (fingertips, palms and soles), acute paronychia, onycholysis, partial or complete loss of nails, pyogenic granuloma-like lesions (nails), brittle nails, excess growth of eyelashes and/or eyebrows, texture change of facial and scalp hair (curly,wavy, fine and brittle), alopecia (pattern or cicatricial), poliosis, mucositis, photosensitivity

modified from (1)

5k

CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: SPECIAL SKIN REACTIONS TO CHECKPOINT INHIBITORS

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KEY MESSAGES

- The development of checkpoint inhibitors targeting PD-1 and CTLA-4 is a major breakthrough in cancer treatment, but associated with immune-related adverse events
- Skin eruptions occur in >30% of patients and are the most frequent immune-related adverse events under checkpoint inhibition
- Rashes, pruritus and vitiligo are most common, however, the spectrum of cutaneous skin reactions is wide also including lichenoid, eczematous, psoriasiform and autoimmune skin disorders
- The majority of these reactions are mild and self-limiting. Only in few cases cessation of checkpoint inhibition is necessary

The use of immune checkpoint inhibitors (CPIs) has tremendously improved the treatment possibilities of advanced malignant melanoma and several other types of cancer. CPIs target either the inhibitory receptor CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4), which is involved in the interaction between antigen presenting cells and T-cells or the inhibitory receptor PD-1 (programmed death 1) interacting between tumor cells and T-cells.

Physiologically these receptors regulate maintenance of self-tolerance and the suppression of excessive immune responses, however, some tumor cells can misemploy these pathways in order to escape immune defence. CPIs restore the function of the immune system to target and kill cancer cells (Figure 1). Currently, two anti-PD-1 antibodies (pembrolizumab and nivolumab) and one anti-CTLA-4 antibody (ipilimumab) have been approved for treatment of advanced malignant melanoma.

Due to their mode of action, immune-related adverse events (irAEs) are the most commonly occurring side effects under CPI treatment with the skin being the most frequently impaired organ.

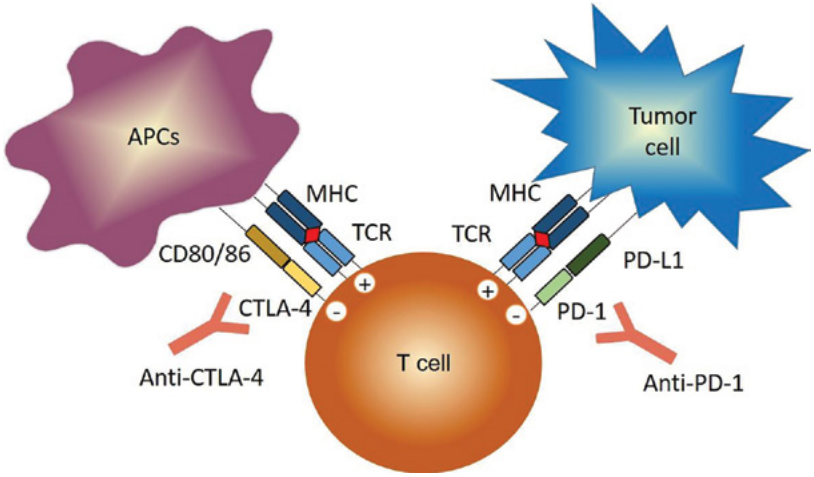

Figure 1 Schematic presentation of mechanism of immune checkpoint inhibitors targeting CTLA-4 and PD-1. MHC = major histocompatibility complex, TCR = T cell receptor, CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4, PD-1 = programmed death 1, PD-L1 = programmed death 1 ligand

TABLE 1

Frequency of cutaneous irAEs under immune checkpoint inhibition

	Anti-PD-1		Anti-CTLA-4	Anti-PD-1 + Anti-CTLA-4
Skin eruption	Pembrolizumab	Nivolumab	Ipilimumab	Nivolumab + Ipilimumab
All	Data missing	34-42%	44-59%	59-72%
Rash	13-21%	13-22%	15-26%	29-55%
Pruritus	14-21%	17-19%	25-36%	33-47%
Vitiligo	9-11%	8-11%	2-9%	7-11%

Modified from Sibaud V. Dermatologic Reactions to Immune Checkpoint Inhibitors: Skin Toxicities and Immunotherapy. Am J Clin Dermatol 2018;19:345-61

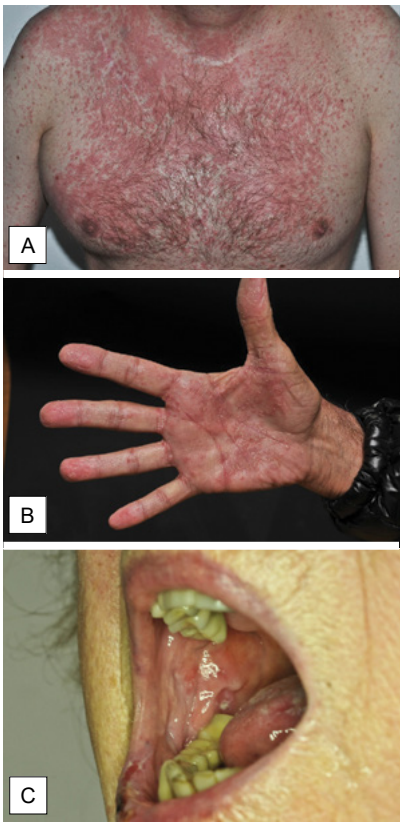

Figure 2 Different typical clinical manifestations of cutaneous immune-related adverse events to checkpoint inhibitor therapy showing a maculopapular exanthem (a) and a psoriasiform dermatitis predominantly in acral areas (b) to pembrolizumab as well as a lichenoid stomatitis (c) to nivolumab

More than thirty percent of patients develop cutaneous side effects. These occur more commonly under combination therapy of ipilimumab and nivolumab compared to CTLA-4 and PD-1 monotherapy (Table 1). The most common cutaneous irAEs are rashes (not otherwise specified), pruritus and vitiligo. However, the overall spectrum of possible cutaneous irAEs is very wide and ranges from e.g. eczematous, psoriasiform and lichenoid reactions via acneiform rashes and alopecia to autoimmune skin disorders (e.g. bullous pemphigoid, vasculitis and dermatomyositis). Extremely rarely, life-threatening cutaneous drug reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis can also occur.

The underlying pathogenesis of cutaneous irAEs is currently not fully understood as the dermal/ epidermal antigens that are targeted aberrantly by unleashed CD4+ and/ or CD8+ T cells currently remain to be identified, but an immune deviation caused by the CPI treatment seems to be essential.

The treatment of cutaneous irAEs depends on the severity of the reaction. Depending on e.g. the affected skin area, occurrence of bullae/ exfoliation or complications and limitation of self-care activities of daily living, cutaneous irAEs can be divided according to the CTCAE criteria into grade one to five. Most skin eruptions are mild and self-limiting. These low-grade irAEs can be treated with topical steroids and antihistamines and do not necessitate discontinuation of immunotherapy whereas the rarely occurring high grade dermatologic toxicities (grade 3 or 4) require application of systemic steroids and potentially permanent discontinuation of immunotherapy.

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CUTANEOUS DRUG HYPERSENSITIVITY REACTIONS: DESENSITIZATION IN CUTANEOUS DRUG HYPERSENSITIVITY

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KEY MESSAGES

- Monoclonal antibodies are part of targeted and personalized medicine. Because they improve the quality of life and survival they are key and essential medications of the XXI
- Hypersensitivity reactions to monoclonal antibodies are unexpected and can be severe including anaphylaxis and prevent patients from first line treatments
- Desensitization is a ground breaking therapeutic approach to IV , SQ and other administration modalities allowing patients to safely and successfully be re-introduced to their allergic medications

Reactions to medications including drug hypersensitivity have increased in the last 10 years with the advent of new and targeted therapeutic biological agents and monoclonal antibodies (MoAbs) directed against molecular targets in personalized medicine. Cutaneous reactions to chemotherapeutic agents, monoclonal antibodies and antibiotics include acute type I reactions such as urticaria, angioedema, flushing and pruritus which can present after one (taxanes and some monoclonal antibodies such as rituximab) or more exposures (beta lactams, platins and some monoclonal antibodies such as trastuzumab, infliximab, cetuximab) and can be associated to other systemic symptoms and anaphylaxis. Delayed type IV reactions which include maculo papular rashes can occur within 1 to 6 hours after the infusion or injection. Patients presenting with such reactions may be forced to abandon first line treatments for fear of more severe reactions upon re-exposure, including anaphylaxis. Rapid drug desensitization is a new therapeutic approach to provide first line therapy for patients in need, to either extend life expectancy and/or improve the quality of life and has been successfully applied to acute and delayed drug induced cutaneous reactions. The inhibitory mechanisms of type I/IgE mediated desensitizations have been described in vitro and in vivo and provide outstanding protecting against anaphylaxis. For severe cutaneous allergic reactions with systemic symptoms (SCARS) including SJS, TEN, DRESS, AGEP and serum sickness there is still little understanding of the pathogenesis and although few anecdotal cases have been publish it is generally not recommended. Desensitization protocols have been standardized with 3-4 diluted bags and a total time of 6-8 hours infusion, with minor reactions in less than 20% of cases and no anaphylaxis . For MoAbs used in subcutaneous injections desensitization protocols have been recently developed such as for omalizumab (Table 2) to address acute reactions. Delayed reactions to etanercept and adalimumab include local injection site reactions (ISR) with erythema, swelling, pruritus or infiltrated plaques, which can occur in up to 37% treated patients and up to 20% adalimumab treated patients (Figure 1). These reactions can be immediate within minutes of the injections or delayed (1 to 6 hours) and can last several days. Skin testing has been used to detect IgE antibodies against adalimumab (50 mg/ml Prick and 1:100 and 1:10 dilutions for ID) and etanercept (25mg/ml

TABLE 1

Monoclonal subcutaneous desensitization protocol for Omalizumab (target 150 mg)					
Step	Time (min)	Concentration (mg/mL)	Volume (mL)	Dose (mg)	Cumulative dose (mg)
1	0	12.5	0.12	1.5	1
2	30	12.5	0.24	3	4.5
3	60	12.5	0.48	6	10.5
4	90	12.5	0.96	12	22.5
5	120	125	0.19	23.75	46.25
6	150	125	0.39	48.75	95
7	180	125	0.44	55	150

Vial concentration 125 mg/mL (150 mg/1.2 mL)
Adaped from Isabwe et al 2018

TABLE 2

Rapid subcutaneous desensitization for the management of local and systemic hypersensitivity reactions to etanercept and adalimumab								
	Etanercept			Adalimumab				
Day 1,2	Dose (mg)	Dilution	Volume administered (mL)	Time (min)	Dose (mg)	Concentration (50 mg/mL)	Volume (mL)	Cumulative dose (mg)
0	0.5	1:100 (0.5 mg/mL)	1	0	0.5	0.5	1	0.5
30	1.0	1:10 (5 mg/mL)	0.2	30	0.75	5	0.15	1.25
60	2	1:10 (5 mg/mL)	0.4	60	1.25	5	0.25	2.50
90	4	1:10 (5 mg/mL)	0.8	90	2.50	5	0.50	5.0
120	8	1:1 (50 mg/mL)	0.16	120	5.0	50	0.10	10
150	9	1:1 (50 mg/mL)	0.18	150	10	50	0.20	20
Total dose	24.5			180	20	50	0.40	40 mg/mL
Day 3								
0	0.50	1:100 (0.5 mg/mL)	1.0					
30	1.00	1:10 (5 mg/mL)	0.2					
60	2.00	1:10 (5 mg/mL)	0.4					
90	4.00	1:10 (5 mg/mL)	0.8					
120	8.00	1:1 (50 mg/mL)	0.16					
150	16.00	1:1 (50 mg/mL)	0.32					
180	18.5	1:1 (50 mg/mL)	0.37					
Total dose	50							

Prick and 1:100 and 1:10 for ID), which have been positive in acute reactions. Delayed reactions have been associated with IgG antibodies and T cell activation and the role of patch testing and delayed reading of prick and intradermal testing has not been conclusive. Desensitization protocols for delayed reactions have been successfully applied in 1 to 3 days and have achieved complete or partial reduction in skin lesions (Figure 2) such that patients have been able to continue on first line therapy.

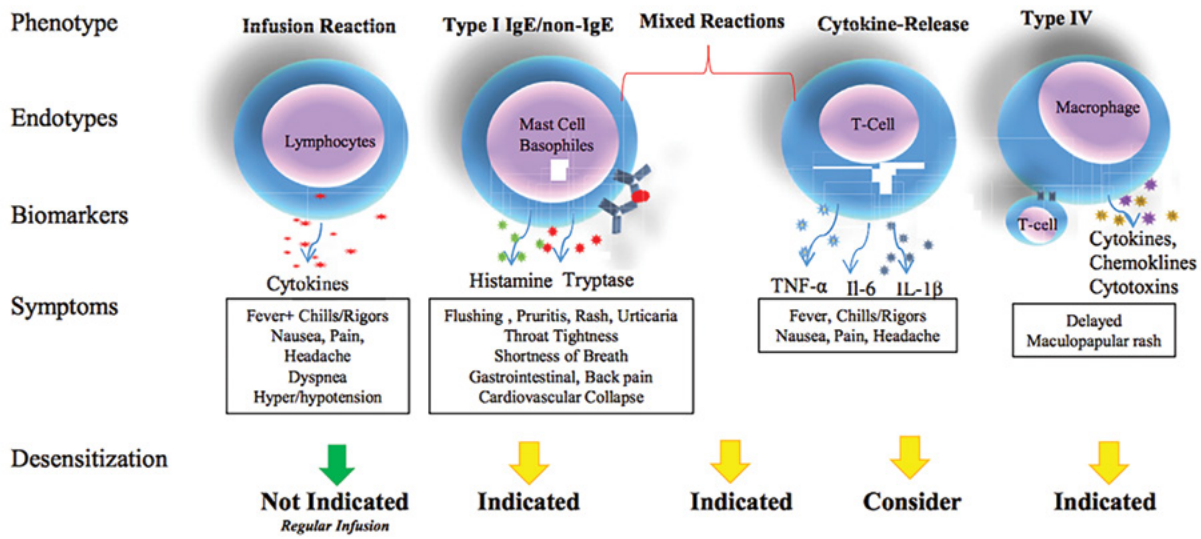

Figure 1 Pathways to drug induced hypersensitivity and their indication for desensitization (Adapted from Isabwe et al 2018)

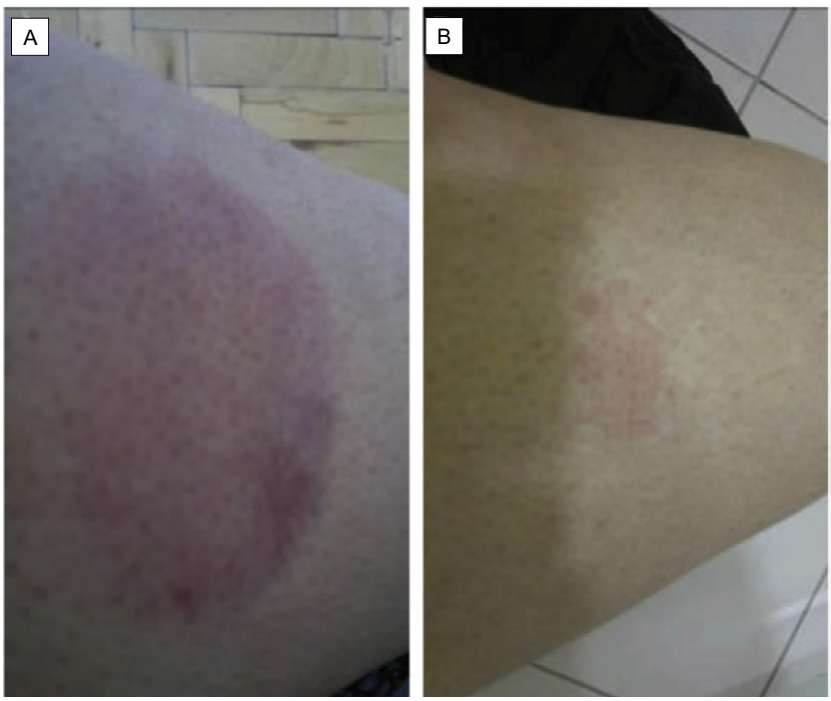

Figure 2 Adapted from Bavbek 6 Injection site reaction with etanercept before (A) and after desensitization (B)

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6a MASTOCYTOSIS: URTICARIA PIGMENTOSA AND MASTOCYTOSIS IN THE SKIN

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Mastocytosis is characterised by accumulation of clonal mast cells (MCs), often related to activating KIT mutations.

In children the disease is typically limited to the skin and symptoms often mild, whereas adulthood-onset mastocytosis is almost always systemic with heterogeneous, potentially severe symptoms, and an increased risk for anaphylaxis, osteoporosis and other complications (Table 1).

The presence of mastocytosis skin lesions in adults is a clear sign of systemic mastocytosis irrespective of presence of extracutaneous symptoms, or level of baseline s-tryptase, and relevant work-up and counselling warranted.

Skin involvement is seen in around 2/3 of adult and all pediatric patients.

Traditionally termed urticaria pigmentosa (UP), reflecting the reddish-brown color of the skin lesions and their ability to wheal and flare upon local MC degranulation, in newer literature the term maculopapular cutaneous mastocytosis has been proposed. Telangiectasia macularis eruptiva perstans was formerly considered a separate entity, but now regarded as a vasodilated UP. In pediatric mastocytosis two other forms of skin involvement are seen; the solitary mastocytoma and diffuse cutaneous mastocytosis.

In adults, UP has a gradual onset and slow progression rate, with flat, well-demarcated, monomorphic, 2-5 millimeters, reddish-brown macules, symmetrically distributed on the trunk and proximal extremities (Figure 1). The extent of skin involvement varies greatly from few, inconspic-

KEY MESSAGES

- Mastocytosis is a heterogeneous disease characterised by accumulation of clonal mast cells. Symptoms relate to infiltration of mast cells in different organs and effects of mast cell mediators
- The disease may affect children as well as adults, and has hitherto been considered rare, but is probably underdiagnosed
- In adults mastocytosis is almost always systemic, and follows a chronic course, with heterogeneous, fluctuating symptoms from skin (itch, whealing, flushing), GI-tract (colicky pain, diarrhea, dyspepsia), bone (osteoporosis, pain), as well as more diffuse symptoms (fatigue, headache, memory problems) and a clearly increased risk for anaphylaxis
- In children symptoms are typically limited to the skin, and the disease typically undergoes a peculiar spontaneous regression before adulthood
- In around 2/3 of adult and all pediatric patients, characteristic reddish-brown skin lesions are seen, traditionally termed urticaria pigmentosa. Darier's sign, defined by a wheal and flare reaction of the skin lesions upon mechanical rubbing, is an important clinical feature and diagnostic finding in patients with cutaneous involvement
- Given the complexity and rarity of the disease it is generally advised that patients with mastocytosis are evaluated in specialised comprehensive care centers

TABLE 1

Comparison of pediatric and adult mastocytosis

	Pediatric mastocytosis	Adult mastocytosis
Typical disease category	Cutaneous mastocytosis	Systemic mastocytosis
KIT D816V mutation	20-30%. Other *KIT* mutations (exon 8, 9, 11) frequent	>90%
Skin lesions	Always present	Present in around 2/3
Typical tryptase level (ng/ml)	< 11.4 (normal)	> 20, but may be normal
Typical course of the disease	Resolution in 3/4 around puberty	Chronic
Symptoms	Typically limited to the skin and manageable by anti-MC mediator treatment	Very heterogeneous, and may be severe and difficult to control
Extracutaneous manifestations	Rare, but GI-symptoms may be encountered	Frequent, including osteoporosis
Risk for anaphylaxis	Low (1-9%)	High (35-50%)
Advanced / aggressive disease	Exceedingly rare	5-10% of patients

uous elements to severe, confluent skin lesions (Figure 1). In addition to being of cosmetic burden to many patients, itch, flushing and whealing is often present and may be elicited by e.g. friction, heat/cold or ultraviolet light exposure.

Darier's sign is an important clinical feature of mastocytosis in the skin. It is best elicited by stroking a skin lesion around 5 times by using moderate pressure with a tongue spatula. Within minutes a wheal-and-flare reaction of the UP lesion will develop. Darier's sign differs from dermographism by not affecting the surrounding, non-lesional skin, and thus a specific diagnostic finding in mastocytosis (Figure 1).

In around 1/3 of adult patients no UP skin lesions are present. Here, the disease presentation is often anaphylaxis (most commonly wasp), and the diagnosis based on elevated baseline s-tryptase, *KIT* D816V mutation analysis in blood and a bone marrow exam.

Pediatric mastocytosis typically starts within the first two years of life, and skin lesions often polymorphic, with larger lesions of variable size and shape, nodular or plaque-type lesions (Figure 1). Itch, flushing or even bullous reactions are most prominent in the first 3-4 years after onset. The skin lesions gradually fade in many children and an apparent spontaneous regression is seen in most cases around puberty.

In adults as well as children, treatment with non-sedating H1-anthistamines may improve skin symptoms. Additional treatment options for mediator related symptoms include H2-blockers, montelukast, chromoglicate and omalizumab. Reflecting a poor understanding of pathophysiologic mechanisms, there is a so far unmet need for non-toxic treatments targeting the UP skin lesions themselves.

Given the complexity and rarity of mastocytosis it is generally advised that patients are evaluated in specialised comprehensive care mastocytosis centers.

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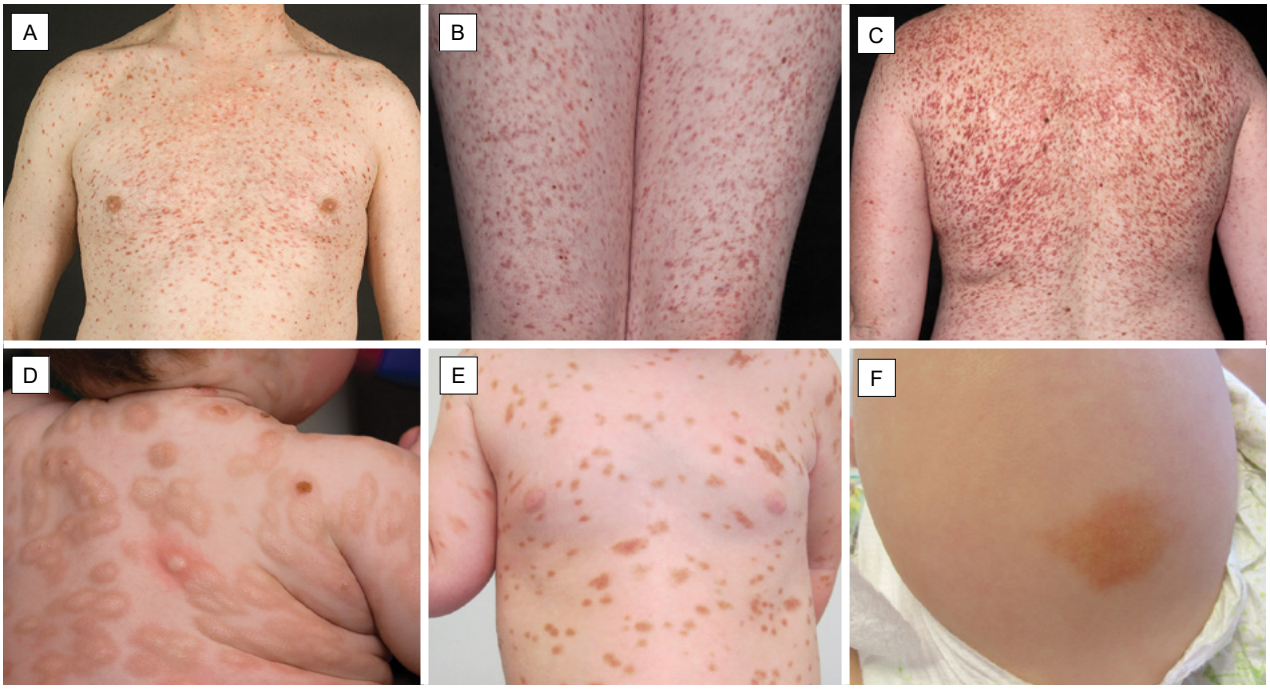

Figure 1 Skin lesions in mastocytosis. A-C: Adulthood-onset mastocytosis showing monomorphic, small urticaria pigmentosa lesions. D-F: Pediatric-onset mastocytosis with nodular skin lesions with Darier's sign (D), polymorphic macular lesions (E), and a solitary mastocytoma (F)

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6b

MASTOCYTOSIS: MASTOCYTOSIS AND ANAPHYLAXIS

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KEY MESSAGES

- The prevalence of anaphylaxis in mastocytosis patients is much higher than the estimated frequency of anaphylaxis in the general population
- The hymenoptera venom sting represents the most common trigger of anaphylaxis in adult mastocytosis patients and after that idiopatic anahylaxis remains one the most common causes of anaphylaxis in mastocytosis patients
- The anaphylactic reactions of patients with mastcytosis and hymenoptera venom allergy are characterized in most of cases by the absence of angioedema and erythema and the predominance of cardiovascular symptoms, such as hypotension leading to loss of consciousness
- Omalizumab has been reported to be safe and effective in preventing recurrent unprovoked anaphylaxis

Mastocytosis is a clonal mast cell disorder characterized by the proliferation and accumulation of mast cells in different tissues, with a preferential localization in the bone marrow and in the skin. Cutaneous Mastocytosis (CM), is usually most frequent in childhood, while Systemic Mastocytosis (SM) mainly affects adults, and involves one or more extra-cutaneous organs (BM, gastrointestinal tract, lymph nods and spleen), with or without skin involvement. The majority of cases of SM show a somatic 'autoactivating' point mutation at codon 816 of kit-receptor gene. Tab 1 The diagnosis of SM is based on major criteria plus one minor criterion, or on three minor criteria Tab 2 It is characterized by symptoms originating from a massive MC activation and release of mediators; anaphylaxis is the most common expression of this situation. In a study, analysing patients presenting with anaphylaxis to an emergency care setting, systemic mastocytosis was diagnosed in 7.7% of adults; flying insects were elicitors in half of these patients.

Moreover, the prevalence of anaphylaxis in mastocytosis patients is reported to be between 22% and 49% in adults, and between 6% and 9% in children, which is much higher than 0.05–2% reported in the general population; in children, the risk is less high and the risk appears to be associated with extensive skin involvement and high serum tryptase levels, and especially during episodes of blistering. The risk for anaphylaxis also appears to be significantly higher in patients with indolent systemic mastocytosis as compared with more advanced forms of mastocytosis.

Hymenoptera stings are the most frequent cause of anaphylaxis in mastocytosis patients (19-60% of cases of anaphylaxis), followed by foods (3-16% of cases) and drugs (5-9%).

Allergic/anaphylactic symptoms after hymenoptera sting are mostly present in patients with an indolent variant of systemic mastocytosis (ISM) without skin lesions, and the anaphylactic reactions of these patients are clinically characterized in most of cases by the absence of angioedema and erythema and the predominance of cardiovascular symptoms, such as hypotension leading to loss of consciousness.

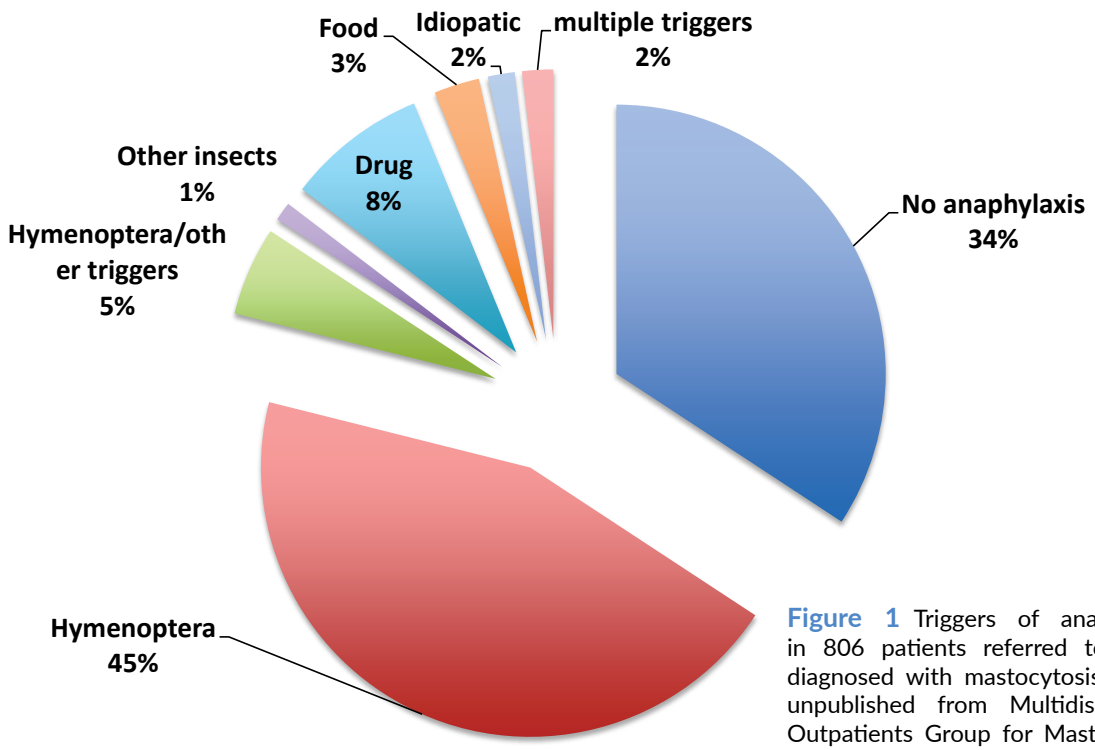

Figure 1 Triggers of anaphylaxis in 806 patients referred to GISM diagnosed with mastocytosis. (data unpublished from Multidisciplinary Outpatients Group for Mastocytosis of Verona GISM 2018)

MANAGEMENT OF MASTOCYTOSIS PATIENTS AND ANAPHYLAXIS

The most important therapeutic approach for patients with mastocytosis and anaphylaxis is to provide them with two **epinephrine self-injectors** and to instruct how to use them.

For those who have confirmed sensitivity to hymenopera sting, **venom immunotherapy** (VIT) represents a safe and effective treatment, which decreases the risk of subsequent systemic reactions and reduces morbidity and mortality. It has been confirmed that patients with mastocytosis and hymenoptera venom allergy, who were protected during VIT, may have very severe reactions after VIT discontinuation, therefore these patients should continue life-long VIT.

Omalizumab is a monoclonal antibody that binds free IgE and reduces the expression of FcεRI on MCs and basophils and is a labelled treatment for allergic asthma and chronic urticaria. More recently in some cases reports, omalizumab appears to be a promising treatment option in SM, effectively preventing anaphylaxis and improving chronic MC mediator-related symptoms, insufficiently controlled by conventional therapy.

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TABLE 1

WHO classification of Mastocytosis		
	Abbreviation	**Definition**
Cutaneous mastocytosis	CM	exclusive involvement of the skin
Indolent SM	ISM	meets criteria for SM. No "C"findings and <2 "B" findings. No evidence of AHN
– Bone Marrow mastocytosis	BMM	ISM sub-variant with bone marrow involvement, but without mastocytosis in the skin (MIS).
Smouldering SM	SSM	as ISM, but with 2 or more "B" findings, and no "C" findings
Aggressive SM	ASM	meets criteria for SM. One or more "C" findings. No evidence of mast cell leukemia
Mast cell leukemia	MCL	meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. BM aspirate smears show ≥20% mastcells. In typical MCL, mast cells account for ≥10% of peripheral blood white cells
Systemic mastocytosis with an associated hematological neoplasm	SM-AHN	all variants of SM associated to an other hematological neoplasm
Mast cell sarcoma	MCS	Localized tumour consisting of highly atypical, immature MC, with destructive growth and metastatic potential

Abbreviations: MC, mast cell(s), AHN, associated hematologic neoplasia; ANC, absolute neutrophil count; Hgb, hemoglobin.

TABLE 2

WHO Diagnostic Criteria for Systemic Mastocytosis (SM)	
The Diagnosis of SM is established when at least one major and one minor or at least three minor criteria are present	
Major	Multifocal dense infiltrates of MC in bone marrow sections or other extracutaneous organ(s) (>15 MCs in aggregate)
Minor	a. MC in bone marrow or other extracutaneous organ(s) show an abnormal (spindle-shaped) morphology (>25%) b. KIT mutation at codon 816 in extracutaneous organ(s). In the majority of cases the mutation is D816V c. MC in bone marrow express CD2 and/or CD25 d. Serum total tryptase >20 ng/ml (does not count in patients who have AHNMD-type disease)
"B" findings	A. BM biopsy showing >30% infiltration by MC (focal, dense aggregates) and/or serum total tryptase level >200 ng/mL B. Signs of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts C. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging
"C" findings	1. Bone marrow dysfunction manifested by one or more cytopenia(s) (ANC <1.0 x 109/L, Hgb <10 g/dL, or platelets <100 x 109/L), but no obvious non-mast cell hematopoietic malignancy 2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension 3. Skeletal involvement with large osteolytic lesions and/or pathological fractures 4. Palpable splenomegaly with hypersplenism 5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates

Diagnosis of: a) Indolent SM (ISM): meets criteria for SM. No "C"findings. No evidence of AHNMD. b) Smouldering SM (SSM): as ISM, but with 2 or more "B" findings, and no "C" findings. c) Isolated Bone Marrow Mastocytosis (BMM): as ISM with bone marrow involvement, but without skin involvement. d) Aggressive SM (ASM): meets criteria for SM. One or more "C" findings. No evidence of mast cell leukemia. e) Mast cell leukemia (MCL): meets criteria for SM. Bone marrow biopsy shows a diffuse infiltration, usually compact, by atypical, immature mast cells. BM aspirate smears show ≥20% mastcells. In typical MCL, mast cells account for ≥10% of peripheral blood white cells.

Abbreviations: MC, mast cell(s); AHNMD, associated clonal hematologic non-mast cell lineage disease; ANC, absolute neutrophil count; Hgb, hemoglobin.

7a URTICARIA AND ANGIOEDEMA: DEFINITION AND CLASSIFICATION OF URTICARIA

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Urticaria needs to be differentiated from other medical conditions where wheals, angioedema, or both can occur as a symptom, for example anaphylaxis, auto-inflammatory syndromes, or hereditary angioedema (bradykinin-mediated angioedema).

Acute urticaria is defined as the occurrence of spontaneous wheals, angioedema, or both for <6 weeks whereas chronic urticaria is characterised by a duration of recurrent or persistent manifestations for longer than 6 weeks. Table 1 presents a classification for clinical use of chronic urticaria subtypes. Two or more different subtypes of urticaria can coexist in any given patient

(A) Wheal in patients with urticaria has 3 typical features:
1. a central swelling of variable size, almost invariably surrounded by reflex erythema,
2. an itching or sometimes burning sensation,
3. a fleeting nature, with the skin returning to its normal appearance, usually within 30 minutes to 24 hours.

(B) Angioedema in urticaria patients is characterized by:
1. a sudden, pronounced erythematous or skin coloured swelling of the lower dermis and subcutis or mucous membranes,
2. sometimes pain, rather than itch.
3. a resolution slower than that of wheals (can take up to 72 hours).

KEY MESSAGES

- Urticaria is a disease characterized by the development of wheals (hives), angioedema, or both
- We recommend against any routine diagnostic measures in acute spontaneous urticaria
- We recommend for only very limited routine diagnostic measures in chronic spontaneous urticaria
- We recommend limiting routine diagnostic measures to determining the threshold of eliciting factors in inducible urticaria subtypes

DIAGNOSIS OF URTICARIA - FIRST STEP

Acute urticaria usually does not require a diagnostic workup, as it is usually self-limited.

In the last two decades, many advances have been made in identifying causes of different types and subtypes of urticaria.

In chronic spontaneous urticaria, among others, autoreactivity including autoimmunity mediated by functional autoantibodies directed against the IgE receptor, pseudo-allergy (non-allergic hypersensitivity reactions) to foods and drugs, and acute or chronic infections (e.g., Helicobacter pylori or Anisakis simplex) have been described.

However, there are considerable variations in the frequency of underlying causes in the different studies. This also reflects regional differences in the world, for example, different traditional diets and different prevalence of infections.

Thus, it is important to remember that not all possible causative factors need to be investigated in all

TABLE 1

Subtypes of chronic urticaria		
Chronic Spontaneous Urticaria (CSU)[1]	**Inducible Urticaria**	**Typical Triggers of Inducible Urticaria**
Spontaneous appearance of wheals, angioedema or both ≥ 6 weeks due to known or unknown causes	**Physical urticarias**	
	Symptomatic dermographism[2]	sheering forces
	Cold urticaria[3]	cold
	Delayed pressure urticaria[4]	vertical pressure
	Solar urticaria	UV-A, UV-B, visible light
	Heat urticaria[5]	heat
	Vibratory angioedema	vibration
	Cholinergic urticaria	exercise, hot showers
	Contact urticaria	exposure to allergens/irritants
	Aquagenic urticaria	water

[1] *Including, for example, autoreactive urticaria, i.e. the presence of mast cell-activating autoantibodies;*
[2] *also called urticaria factitia, dermographic urticaria;*
[3] *also called cold contact urticaria;*
[4] *also called pressure urticaria;*
[5] *also called heat contact urticaria.*

TABLE 2

The urticaria activity score (UAS) is assessed for every day by the patient himself for the last 24h and can be summed up for one week (UAS7) for assessing disease activity in CSU for longer periods as the disease is fluctuating		
Score	**Wheals**	**Pruritus**
0	None	None
1	Mild (<20 wheals/24 h)	Mild (present but not annoying or troublesome)
2	Moderate (20-50 wheals/24 h)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (>50 wheals/24 h or large confluent areas of wheals)	Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)

patients and the first step in diagnosis is a thorough history.

DIAGNOSIS OF URTICARIA - SECOND STEP

The second step of the diagnosis is the physical examination of the patient. This should include a diagnostic provocation test including drug, food, and physical tests where it is indicated by history. All subsequent diagnostic steps will depend very much on patient history and on the nature of the urticaria subtype. In chronic inducible urticaria unlike CSU it needs to be known that the cause is still largely unknown and therefore it is not recommended to use any routine diagnostic measures but it is strongly recommended to identify the trigger and the threshold to be better able to inform the patient about avoidance measures.

URTICARIA ACTIVITY SCORE

Disease activity in spontaneous urticaria should be assessed both in clinical care and trials with the UAS (Table 2), a unified and simple scoring system.

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7b URTICARIA AND ANGIOEDEMA: DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

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KEY MESSAGES

- In acute urticaria, routine diagnostic procedures are not suggested except that the patient history renders a specific suspicion of underlying allergy, e.g., intake of food or drugs
- In chronic spontaneous urticaria, recommended routine diagnostic tests are differential blood count and erythrocyte sedimentation rate and/or C-reactive protein levels
- In patients who have wheals with or without angioedema, urticarial vasculitis is the main differential diagnosis. In patients with wheals only, autoinflammatory disorders including Schnitzler's syndrome need to be ruled out
- In chronic inducible urticaria (CIndU), provocation tests are used as routine diagnostic workup to identify the subtypes of CIndU and to determine trigger thresholds

The diagnostic approaches are similar for both pediatric and adult urticaria patients. Acute urticaria is self-limiting and does not usually require routine diagnostic workup. However, allergy tests may be useful if type I hypersensitivity, e.g. to food or drugs, is suspected.

In chronic urticaria, the diagnostic workup is aimed at (i) excluding differential diagnoses, (ii) identifying relevant triggers and/or underlying causes, and (iii) assessing disease activity, impact, and control (Figure 1). In patients who display angioedema (AE) without wheals, bradykinin-mediated AE should be excluded. In patients with wheals only, autoinflammatory disorders including Schnitzler's syndrome need to be ruled out. In patients who have wheals with or without AE, urticarial vasculitis (UV) is the main differential diagnosis.

UV is a difficult-to-treat condition characterized by long-lasting urticarial rash and histopathologic findings of leukocytoclastic vasculitis (Figure 2). A punch biopsy of a lesion should be performed to exclude UV in patients in whom individual urticarial lesions persist for more than 24 hours and who have other features of UV listed in Table 1.

A detailed history and physical examination are essential for revealing exacerbating triggers and underlying causes in patients with chronic urticaria. The following important items should be taken into consideration: (i) time of onset of disease, (ii) characteristics of wheals (e.g., duration), (iii) presence of AE, (iv) associated symptoms (e.g., fever), (v) family history of urticaria and AE, (vi) occurrence in relation to possible triggers (e.g., NSAIDs, stress, physical agents etc), (vii) comorbid diseases, and (viii) response to previous therapy. Validated instruments should be used for assessment of chronic spontaneous urticaria (CSU) activity (UAS7, AAS), quality of life (CU-Q2oL, AE-QoL) and control (UCT).

In CSU, the guideline-recommended routine diagnostic tests are differential blood count as well as erythrocyte sedimentation rate and/or C-reactive protein levels. Further diagnostic procedures can be considered if indicated by patient history including avoidance of suspected triggers, search for infections, malignancy, autoimmune thyroid disease, concomitant chronic inducible urticaria (CIndU), and functional autoantibodies. Type I allergy is a rare

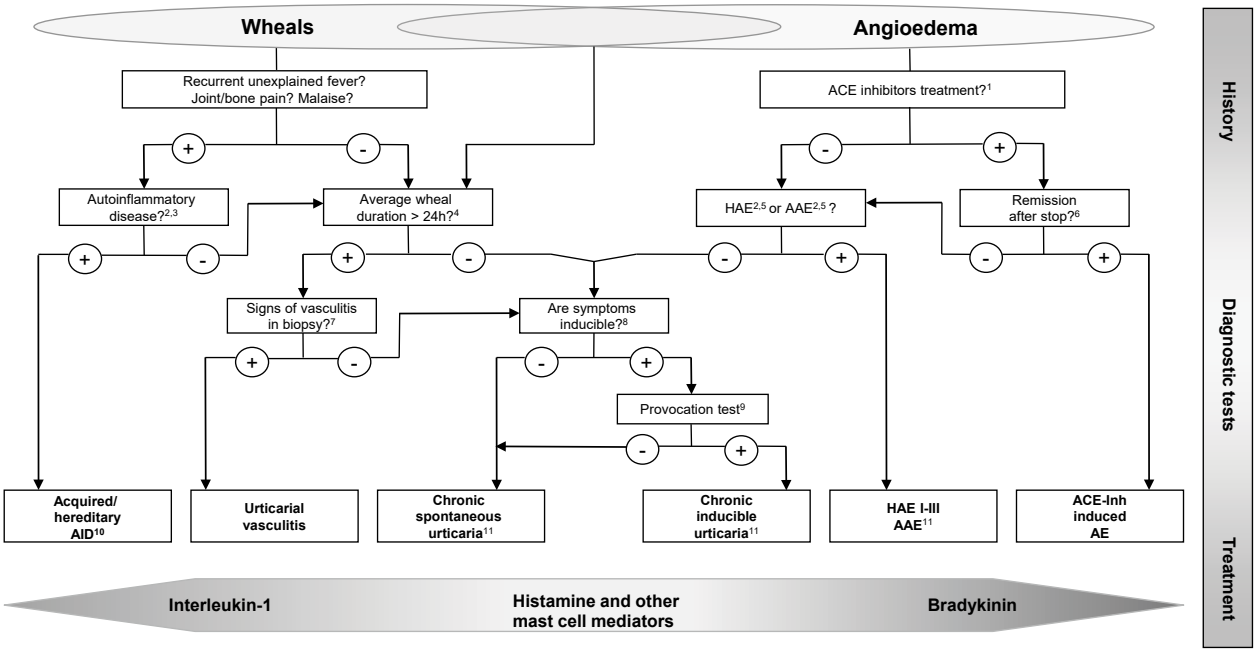

Figure 1 Recommended diagnostic algorithm for chronic urticaria. Diagnostic algorithm for patients presenting with wheals, angioedema or both. AAE: Acquired angioedema due to C1-inhibitor deficiency; ACE-Inh: angiotensin converting enzyme inhibitor; AE: angioedema; AID: Autoinflammatory disease; HAE: Hereditary angioedema. [1] Apart from ACE-inhibitors, other renin inhibitors and sartans have been described to induce angioedema but much less frequently. [2] Patients should be asked for a detailed family history and age of disease onset. [3] Test for elevated 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. [4] Patients should be asked: "For how long does each individual wheal last?" [5] Test for complement C4, C1-INH levels and function; in addition test for C1q and C1-INH antibodies, if AAE is suspected; do gene mutation analysis, if former tests are unremarkable but patient's history suggests hereditary angioedema. [6] If there is no remission after 6 months of ACE-inhibitor discontinuation C1-inhibitor should be tested for. [7] 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 urticarial vasculitis? [8] Patients should be asked: "Can you make your wheals come? Can you bring out your wheals?" [9] In patients with a history suggestive of inducible urticaria standardized provocation testing according to international consensus recommendations should be performed. [10] Acquired AIDs include Schnitzler´s 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). [11] 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. (*Reproduced from Zuberbier T, Aberer W, Asero R, et al. Allergy 2018; 73(7):1393-1414; with permission from Wiley-Blackwell*)

cause of CSU. However, pseudoallergic reactions to NSAIDs or food may appear. Several studies showed CSU remission or improvement after treatment of malignancy, infection (e.g. *Helicobacter pylori*, focal bacterial infection) and hyper- and hypothyroidism. Concomitant CIndU adds to the burden of disease and quality of life impairment. Basophil activation tests and autologous serum skin test can help to diagnose autoimmune CSU associated with IgG-anti-FcεRI/IgE antibodies.

In CIndU, provocation tests are used as routine diagnostic workup to identify the subtypes of CIndU and to determine trigger thresholds (Figure 3). The latter allows assessing disease activity and response to treatment. Examples include tests with a dermographometer (symptomatic dermographism), ice cube (cold urticaria), and pulse-controlled ergometry (cholinergic urticaria).

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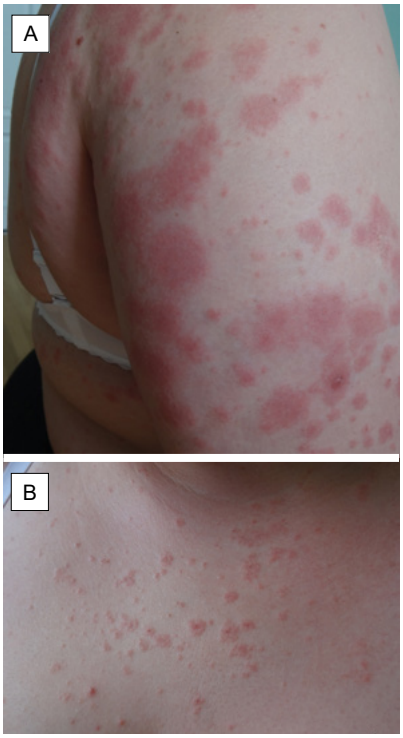

Figure 2 Urticarial lesions on the right arm (A) and the trunk (B) in a female adult patient with urticarial vasculitis

TABLE 1

Differential diagnosis between urticaria and urticarial vasculitis

Parameters	Urticaria	Urticarial vasculitis
Frequency: acute (≤6 weeks) vs chronic (>6 weeks) disease	Acute > chronic	Acute < chronic
Pain and/or burning of the skin	–	+
Itching	+	+/–
Duration of each individual wheal	<24 hours	>24 hours
Resolution of lesions	Complete	Residual signs[3]
Angioedema	+/–	+/–
Systemic symptoms[1]	–	+
Decreased blood levels of complement components	–	+ (in >50%)
Leukocytoclastic vasculitis on lesional skin biopsy[2]	–	+
Underlying disorder	– (rarely)	+ (in >20%)[4]
Efficacy of antihistamines	+/–	–

–: usually absent or rarely effective; +: often present or effective; [1] e.g. joint pain, fever, abdominal pain; [2] erythrocyte extravasation, vascular and perivascular infiltration of polymorphonuclear leukocytes with formation of nuclear dust (leukocytoclasis) and/or fibrinoid necrosis of the vessel walls; [3] purpura or hyperpigmentation; [4] mostly SLE (11%), malignancy (7%), and chronic hepatitis C (3%)

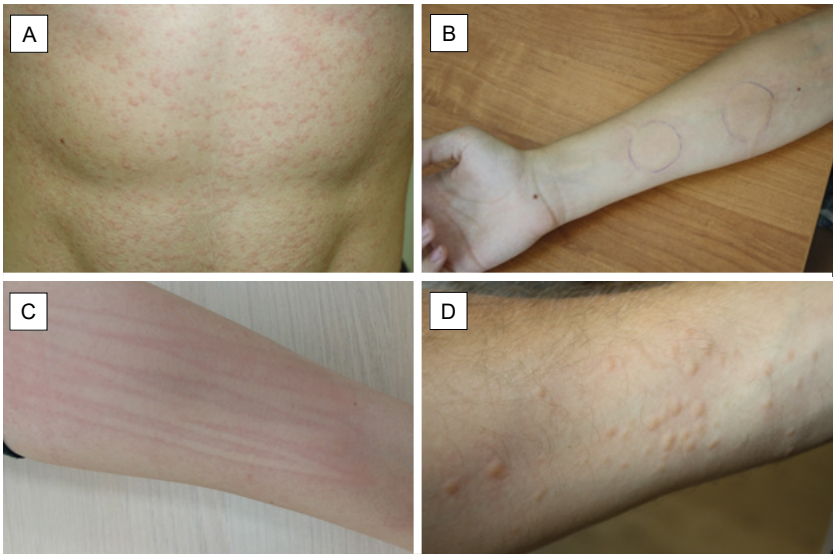

Figure 3 Diagnosis of chronic inducible urticaria. A – Cholinergic urticaria (a 18–year-old male patient, 10 minutes after physical exercise); B – Cold urticaria (a 17-year-old female patient, 10 minutes after test with ice cubes); C – Symptomatic dermographism (a 26-year-old female patient, 5 minutes after stroking of the skin); D – Contact urticaria (a 33-year-old male patient, 5 minutes after contact with a plant, *Urtica dioica*)

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7c

URTICARIA AND ANGIOEDEMA: URTICARIAL AUTOINFLAMMATORY SYNDROMES

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KEY MESSAGES

- Urticarial autoinflammatory diseases are rare differential diagnoses of chronic urticaria
- Prototype autoinflammatory diseases include the hereditary Cryopyrin-associated periodic syndrome and acquired Schnitzler's syndrome
- Disease pathogenesis is mediated via inflammasome activation and interleukin-1ß-driven inflammation in the majority of diseases

Systemic autoinflammatory diseases (sAIDs) are rare chronic and disabling disorders that are predominantly mediated via innate immune pathways. Autoantibodies and antigen-specific T cells - typical features of autoimmune disorders - are absent. SAIDs can be classified into hereditary and complex acquired disorders. Prototype sAIDs are the hereditary Cryopyrin-associated periodic syndrome (CAPS) and acquired Schnitzler's syndrome (SchS). Their prevalence is widely unknown. Estimated frequencies range from 1-3 per million for CAPS to ca. 300 reported cases for SchS. Usually, sAIDs present with a significant morbidity and persist for life. Due to limited awareness, sAIDs are often associated with a considerable delay in diagnosis. Disease onset in CAPS is mostly in early childhood as opposed to late onset in SchS, which starts around the age of 50 years.

Clinical manifestations include chronic urticarial rash and a variety of systemic symptoms such as recurrent fever, malaise, joint and bone pain, ocular and neurologic manifestations. Long-term complications consist of amyloidosis, hearing loss and destructive arthropathy (CAPS) as well as malignant lymphoma (SchS). In contrast to chronic spontaneous urticaria, the wheals or erythematous plaques in CAPS and SchS are non- or only mildly pruritic, and show a circadian rhythm with maximum intensity in the evening (Figure 1). Also angioedemas are usually absent in sAIDs. Histopathology of lesional skin typically demonstrates neutrophil-rich dermal infiltrates (Figure 2). Apart from CAPS and SchS, urticarial or erythematous rash also occurs in a number of other sAIDs presented in Table 1.

Disease pathogenesis in CAPS, a direct inflammasomopathy, is mediated via a gain-of-function mutation in the gene encoding for nucleotide binding like receptor protein 3 (NLRP3). NLRP3 is part of the inflammasome, a cytosolic multi-protein complex, which controls the activity of cytokines interleukin-1ß (IL-1ß) and IL-18. The NLRP3 mutation in CAPS results in an over-activated inflammasome followed by cytokine-driven inflammation. Within the spectrum

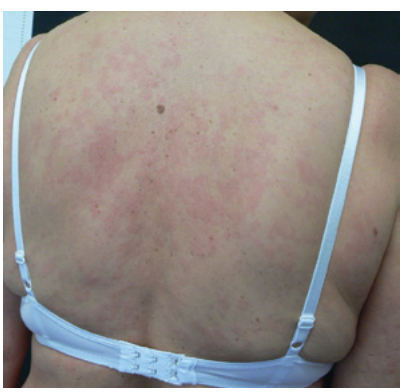

Figure 1 Urticarial rash in a 50-year-old female patient with SchS

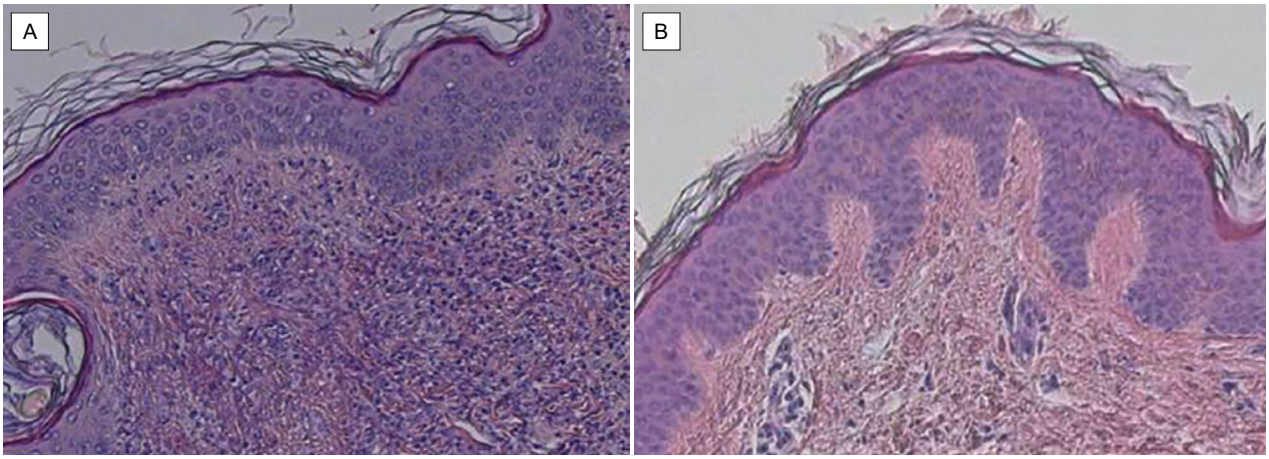

Figure 2 Skin histology. A) Routine histology (H.E.) of SchS lesional skin shows dense dermal infiltrate of mainly neutrophils. B) Routine histology of chronic spontaneous urticaria skin shows only few infiltrating lympho-histiocytic cells. Original magnification 50x

TABLE 1

Autoinflammatory diseases presenting with urticarial rash	
Monogenic diseases (acronym) [*gene*]	**Complex diseases (acronym)**
Cryopyrin-associated periodic syndrome (CAPS) [*NLRP3*]	Schnitzler's syndrome (SchS)
Familial cold autoinflammatory syndrome 2 (FCAS 2) [*NLRP12*]	Adult-onset Still's disease (AOSD) / Systemic juvenile idiopathic arthritis (SJIA)
NLRC4-associated macrophage activation syndrome (NLRC4-MAS) [*NLRC4*]	Neutrophilic urticarial dermatosis (NUD)
Phospholipase Cγ2-associated antibody deficiency (PLAID) [*PLCG2*]	
Mevalonate kinase deficiency (MKD) [*MVK*]	
TNF-R-associated periodic syndrome (TRAPS) [*TNFRSF1 A*]	

of sAIDs, the pathogenesis of acquired disorders is less well-known. The quick and drastic effect of IL-1 inhibition in patients and its dysfunctional inflammasome components assign SchS to the group of inflammasomopathies too.

Pathophysiologic insights resulted in the development of specific cytokine-targeted drugs for sAIDs. Within these, IL-1 blockers are the most common therapies and they are also currently approved for the use in CAPS, other hereditary fever syndromes and (adult-onset) Still's disease. Clinical studies with IL-1 blockers in CAPS, SchS and further sAIDs revealed a good and rapid response of clinical symptoms and normalization of inflammation markers in treated patients. Still, the lack of availability of approved therapies is a problem in many of these rare indications including SchS.

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7d

URTICARIA AND ANGIOEDEMA: CONTACT URTICARIA

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KEY MESSAGES

- It consists on the rapid appearance of wheals and flare on the skin that has been in contact with a substance
- Could be immunologic or non-immunologic contact urticaria
- Immune CU could be the first symptom of a systemic allergic reaction

Contact urticaria (CU) consists of the onset of pruritic hives within 30 minutes on skin that has been in contact with the culprit protein or substance. It resolves in minutes or hours without residual skin lesion. When it emerges in the context of an allergic sensitization, it could be the first symptom of a systemic reaction. It was first described in 1973 by Fisher.

Two types of contact urticaria have been recognized (Table 1):

- **Immune CU**: this type of CU is mediated by IgE, requires a previous sensitization and is mediated by mast cell degranulation. It could be triggered by any allergen, usually large molecular weight molecules. Small molecules are believed to act as haptens carried by larger proteins (Figure 1).
- **Non-immune CU**: the so-called non-immune CU has the exact same skin lesions as the immune CU and is the most frequent. It occurs without previous sensitization and does not respond to antihistamines. Because of a good response to NSAIDs it is believed to be mediated by prostaglandins and provoked by substances with vasogenic properties (Figure 2).

CU should be distinguished from protein contact dermatitis (Figure 3), described by Hjorth and Roed-Petersen as the onset of eczema lesions upon contact with certain proteins, and usually affecting fingertips and hands. It could mimic CU because protein contact dermatitis starts several hours after substance skin contact, by erythema and wheals, followed after two days by vesicles and the typical subsequent eczema lesions. However, it tends to appear after 24 hours.

CU is a relevant occupational disease. It is responsible for between 5-10% of occupational skin conditions. The annual incidence is calculated as 0.3-6.2 cases per 100.000 workers/year. Food industry, agriculture, farming, health care, pharmaceutical, and laboratory workers, hairdressers, veterinarians, and bakers are among the most frequently affected by occupational CU.

DIAGNOSIS

The diagnosis of CU is mainly based on a careful history and physical examination. Immune CU should be diagnosed through skin prick test, prick-prick test in the case of certain foods, and by measuring specific IgE against the culprit allergen.

In the case of non-immune CU, an "open test" by applying and gently rubbing the upper back or the extension arm skin with the suspected substance should be performed. A positive reaction is observed within 15-20 minutes. When testing non-standardized substances, these should be priorly tested in a group of healthy controls. Antihistamines and NSAIDs should be avoided 48-72 hours prior to the test. In the case of Immune CU in the context of an

TABLE 1

Differences between immunologic and non-immunologic CU

	Immunologic CU	Non-immunologic CU
	Requires previous sensitization	Without previous sensitization
Onset	Onset before 30 minutes	Usually from 45 minutes
Pathogenesis	IgE mediated, mainly mediated by histamine	Unknown, vasogenic mediators, prostaglandins
Treatment	Antihistamines	Non response to antihistamines, some response to NSAIDS
Other symptoms	Could evolve to generalized urticaria or systemic allergic reaction	Is confined to the skin
Frequently involved substances	Food proteins, animal dander, natural rubber latex	Biocides, fragances, topical drugs, plants, DMSO, ammoniumm persulfate, etc

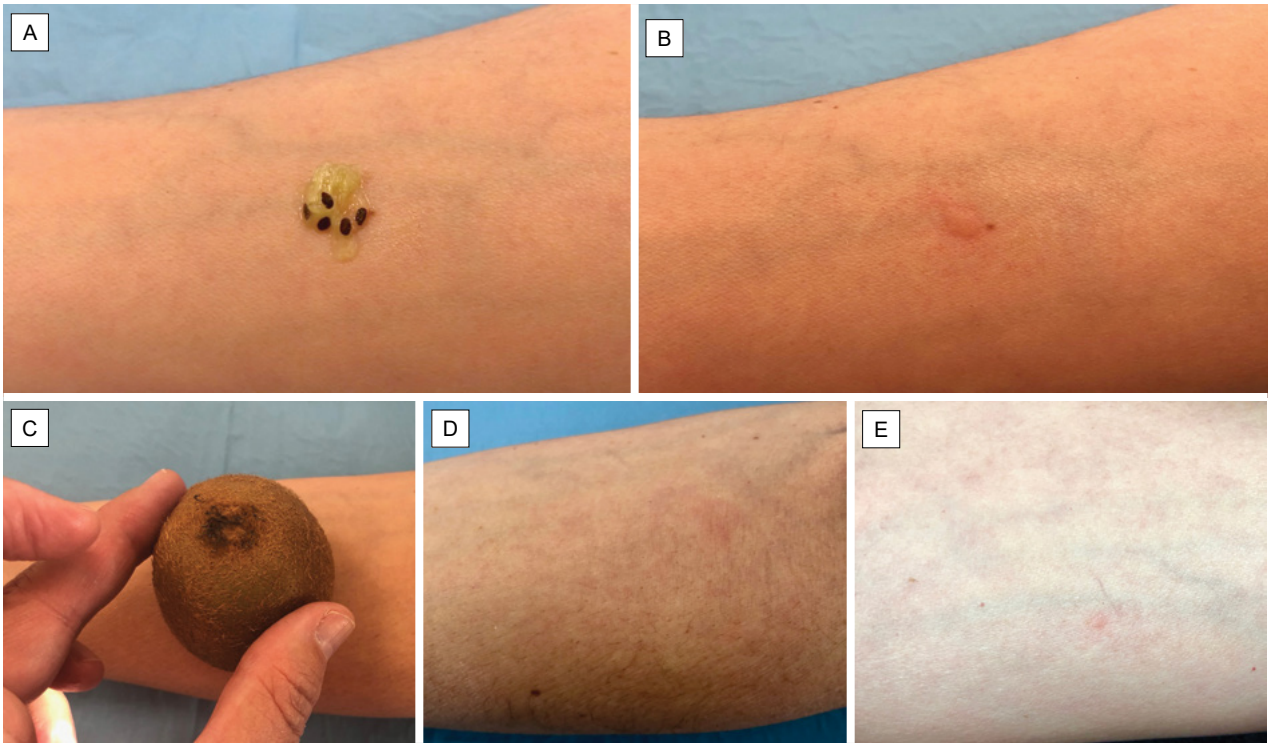

Figure 1 Immune contact urticaria in a patient with anaphylaxis due to kiwi food allergy. Positive prick-prick test (A, B). After gentle rubbing kiwi fruit on the forearm, contact urticaria developed in 10-15 minutes (C, D, E), the reaction was stopped before further evolving because of the risk of developing anaphylaxis

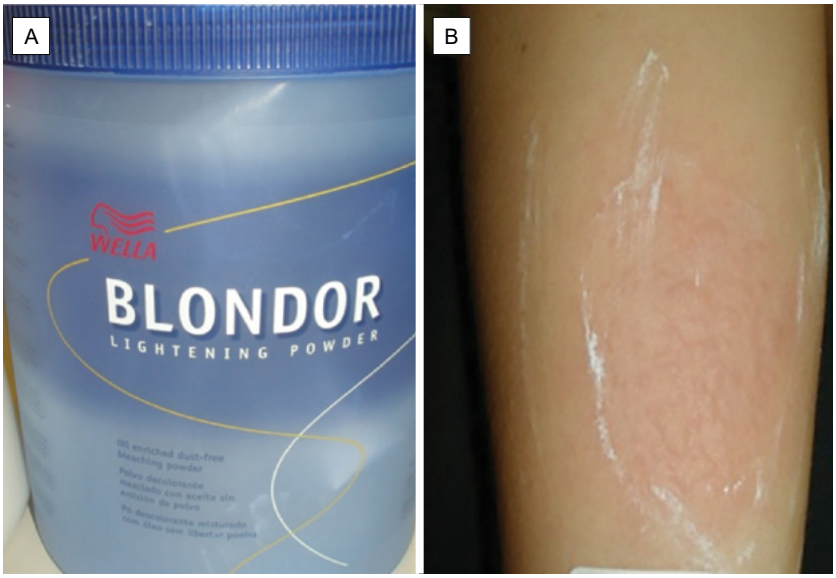

Figure 2 Non-immune contact urticaria due to hair decoloring product (A) probably due to Ammonium persulfate. After rubbing with the prepared product, hives and flare developed within minutes on the skin (B). (*Images courtesy of Dr. Esther Serra, MD*)

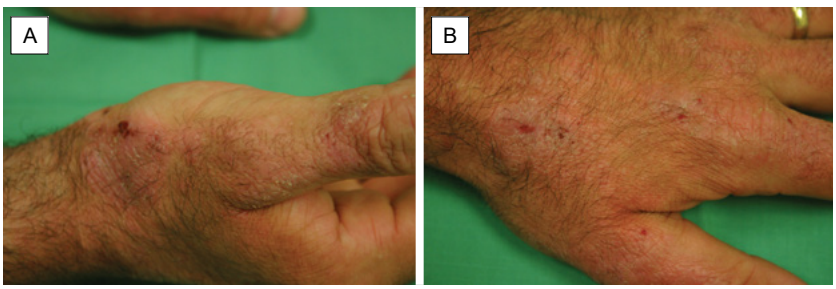

Figure 3 Protein contact dermatitis. Baker with rhinitis and asthma due to wheat allergy. He also develops hands eczema lesions after 24 hours of flour contact.

allergic sensitization with other symptoms, this test should not be performed.

TREATMENT

The treatment is avoidance and educating the patient in order to comply with the avoidance measures. When prevention is not feasible, depending on the type of CU, pharmacologic symptomatic treatment could be recommended.

In the case of occupational CU, apart from primary and secondary preventive measures elimination, substitution and reduction of the skin exposure to the culprit substance is the treatment.

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7e URTICARIA AND ANGIOEDEMA: WHEN TO SUSPECT ALLERGIC URTICARIA

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KEY MESSAGES

- Chronic urticaria is rarely allergic
- Acute urticaria is often elicited by acute infection, especially in children
- Allergic urticaria should be suspected especially when symptoms and signs from other organ systems are present concomitantly, but may be seen alone

Although the majority of patients and their relatives suspect allergies (to e.g. gluten or milk, - or even detergents or food additives (which are not even allergens))- as the underlying cause for their recurrent or chronic hives in urticaria, a true type 1 allergy is only occasionally the eliciting factor.

Allergic urticaria belongs together with the physical urticarias to the group of inducible urticarias, where an external (directly applied to the skin) or internal (oral intake or injection) stimulus is mandatory for elicitation of the hives (Table 1).

External allergic stimuli classically include contact urticaria elicited by proteins in latex or animal saliva but also application of small hapten molecules, such as chlorhexidine can elicit an IgE-mediated response in the skin. It is, however, important to realize, that non-immunologic contact urticaria and physical urticarias are much more frequent than true IgE mediated contact urticaria.

Internal elicitors of allergic urticaria include oral intake of food and drugs together with parenteral injection of drugs or insect venoms.

Especially in children, viral or bacterial infections are frequent elicitors of acute urticaria, but unfortunately very little solid data have been published on epidemiology and phenotypic manifestations of urticaria in relation to infections. Further, a proportion of patients with acute infections are treated with antibiotics and/or pain killers (Aspirin or NSAID) giving rise to suspicion of a drug-induced urticaria rather than hives associated with the infection.

In clear cut cases, the diagnosis of allergic urticaria is easy: a patient with contact urticaria on the hands and forearms while using la-

TABLE 1

Inducible urticarias		
Systemic Type 1 Allergens	**Local contact allergens**	**Physical stimuli and others**
• Foods • Drugs • Insect Venoms	• Latex • Chlorhexidine • Animal saliva • Foods • Drugs	• Cold • Heat • Pressure • Vibration • Viral or bacterial infections
Immediate reactions except in selected cases	Local reaction confined to application site, but may be generalized	

TABLE 2

Important information to look for in the case history	
Characteristic for allergic urticaria	**Not characteristic for allergic urticaria**
• Clear exposition • Clear time relation between exposition and reaction • Patient with other known allergies • Other concomitant allergic symptoms and signs – anaphylaxis?	• Fever • Joint or muscle complaints • Neutrophilia • Physical stimuli necessary • Daily wheals
Confounders	
• Non immunological causes mimicking allergy (mostly contact urticarias) • Cofactors (exercise, drugs, alcohol, menstruation, stress) • More than one culprit (e.g. infection and a drug) • Hidden allergens (excipients in drugs, non-declared substances in food e.g. hydrolysates)	

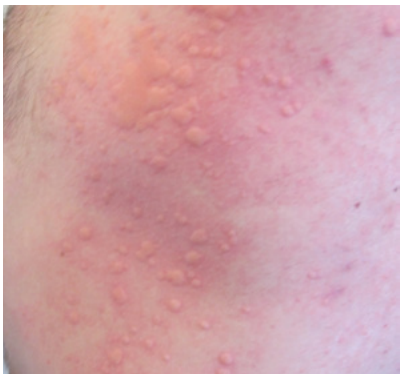

Figure 1 Wheat-dependent exercise-induced anaphylaxis (WDEIA) acute urticaria

tex gloves or a patient, developing generalized urticaria while eating peanuts, normally present little diagnostic challenge to the physician. Especially food induced, allergic urticaria is further associated with other allergic symptoms and signs from the respiratory or gastrointestinal organs. Whereas the urticaria is virtually never elicited by an allergen in the case of daily wheals (chronic spontaneous urticaria), individual acute episodes in association with contact to a potential trigger should alert for a possible allergy as the cause of the urticaria and should lead to a meticulous history taking and allergy testing (Table 2).

There are, however, numerous pitfalls to be taken into account: hives may develop 4-6 hours after intake of a food in the alpha-gal syndrome, on the 4th to 7th day on penicillin treatment or may be elicited by hidden allergens in food. Yet another confounder which also should be considered when obtaining the patient's case history is the presence of cofactors such as exercise, drugs, alcohol or infections. In these cases, allergic urticaria only arises when the culprit food (most often wheat) is ingested in the presence of cofactors, most often exercise (Figure 1).

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7f

URTICARIA AND ANGIOEDEMA: MANAGEMENT OF CHRONIC URTICARIA AND ANGIOEDEMA (EXCLUDING BRADYKININ-INDUCED)

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KEY MESSAGES

- Chronic urticaria (CU) is common and manifests with recurrent wheals, angioedema, or both
- The aim of treating patients with CU is to control the disease, until spontaneous remission occurs
- Treatment responses should be assessed by use of the urticaria control test (UCT)
- The guideline treatment algorithm should be used to achieve disease control: non sedating antihistamine -> omalizumab -> cyclosporine

MANAGEMENT OF CHRONIC URTICARIA AND ANGIOEDEMA

Chronic urticaria (CU) is a common disease characterised by recurrent wheals, angioedema, or both that develop spontaneously (in chronic spontaneous urticaria, CSU) or are induced by definite triggers (chronic inducible urticaria, CIndU), for longer than 6 weeks. CU usually lasts for several years and results in significant quality of life impairment. The recent update and revision of the international EAACI/GA²LEN/EDF/WAO guideline for urticaria provides helpful recommendations on the management of CU.

The aim of treating patients with CU is to control the disease, to provide patients with treatment that prevents the development of wheals and angioedema. To help with this, it is useful to work with standardized tools for assessing disease activity, impact and control. In the case of CSU, the two most important tools are the urticaria activity score (UAS) and the urticaria control test (UCT). For CIndUs, provocation tests should be performed to assess trigger thresholds and disease activity of patients.

The revised and updated version of the international EAACI/GA²LEN/EDF/WAO guideline for urticaria provides a treatment algorithm that should be used in all patients with CU (Figure 1). All CU patients should first receive a non-sedating antihistamine, daily. If this does not result in disease control, the antihistamine is to be updosed, up to four times the standard dose. In patients resistant to high dose antihistamine treatment, omalizumab is the treatment of choice. Patients who do not respond to omalizumab should be treated with cyclosporine.

Today, several non-sedating antihistamines are available and suitable for long-term use. These antihistamines can be given at higher than standard doses without causing sedation. Omalizumab, which is licensed for the use in patients with CSU, reduces IgE levels and, subsequently, IgE receptor expression. Both of these effects are relevant for clinical efficacy. In patients with mast cell-activating autoantibodies directed against the IgE receptor, treatment responses may be delayed. Low baseline IgE levels are linked to higher levels of non response. Both, antihistamines and omalizumab, should be used for as long as it takes for CU to go into remission.

New treatment options for CU are under development. These include modulators of mast cell activation and novel IgE-targeting strategies. The implementation of the recommendations of the revised

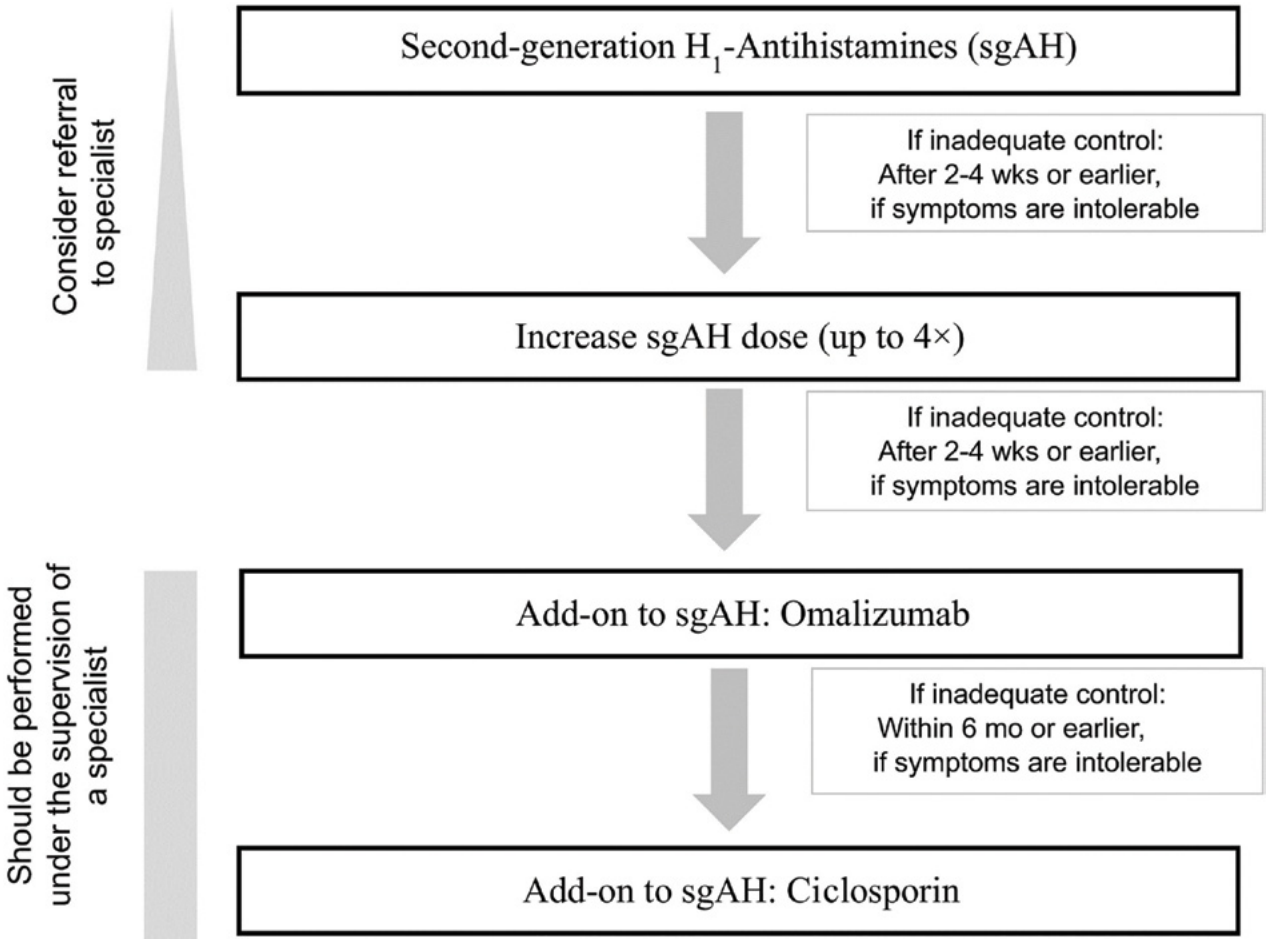

Figure 1 The treatment algorithm for patients with chronic urticaria as recommended by the current EAACI/GA²LEN/EDF/WAO guideline for urticaria (1)

and updated international EAACI/GA²LEN/EDF/WAO guideline for urticaria can help to improve the management of CU.

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8a SKIN MANIFESTATIONS IN FOOD ALLERGY

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Allergic reactions to foods very often manifest in the skin. Acute urticaria and angioedema are the most common cutaneous manifestations of food allergy (FA), but also atopic dermatitis (AD), contact urticaria and protein contact dermatitis are examples of skin symptoms associated with FA (Table 1).

IgE MEDIATED CUTANEOUS MANIFESTATIONS OF FOOD ALLERGY

Urticaria is characterised by fleeting wheals with localised intracutaneous edema and surrounding flare, each lasting 1-24 hours, angioedema lasting up to 72 hours. In IgE-mediated FA, specific IgE to the eliciting food is bound to mast cells in the skin. Upon intake of the offending food, the food allergen cross links these IgE molecules causing mast cell activation and degranulation. The subsequent release of vasoactive mediators leads to urticaria and/or angioedema within minutes to two hours after ingestion of the culprit food. Urticaria (Figure 1) and angioedema (Figure 2) are the most worrying cutaneous manifestations of food allergy since these symptoms may be the first signs of possible life-threatening anaphylaxis.

KEY MESSAGES

- The skin is one of the most targeted organs in food allergic reactions
- Common cutaneous manifestations of food allergy include urticaria, angioedema, atopic dermatitis, contact urticaria and protein contact dermatitis
- Atopic dermatitis is rarely caused by food hypersensitivity, but especially in early childhood the two clinical entities often co-exist. The presence of food allergy should particularly be looked for in infants/children diagnosed with atopic dermatitis at a young age
- A suspicion of food allergy should always prompt a thorough diagnostic evaluation to verify the diagnosis and to avoid unnecessary dietary restrictions

TABLE 1

Common cutaneous manifestations of food allergy

Type	Mechanism	Timing of reaction	Diagnostic approaches
Urticaria/ angioedema	IgE-mediated	Immediate	Skin prick test, food specific IgE, food challenges
Contact urticaria	IgE mediated or direct mast cell stimulation	Immediate	Skin prick test, specific IgE, open application test, food challenges (if oral tolerance is not known)
Atopic dermatitis	IgE mediated and/or cell mediated	Immediate and/or delayed	Skin prick test, food specific IgE, food challenges
Protein contact dermatitis	IgE mediated/ cell mediated	Immediate/ delayed	Skin prick test, food specific IgE

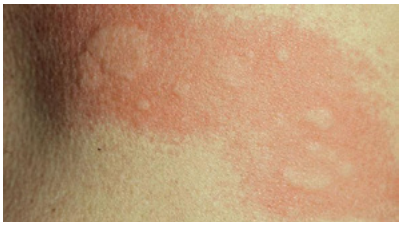

Figure 1 Urticaria is the most common cutaneous manifestation of food allergy (*courtesy of Danderm by Professor Niels K. Veien, Denmark*)

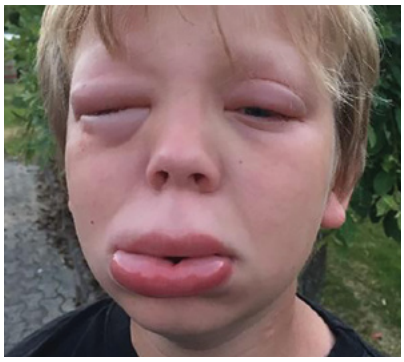

Figure 2 Angioedema is often seen in combination with urticaria (*shown with written consent from the patient and parents*)

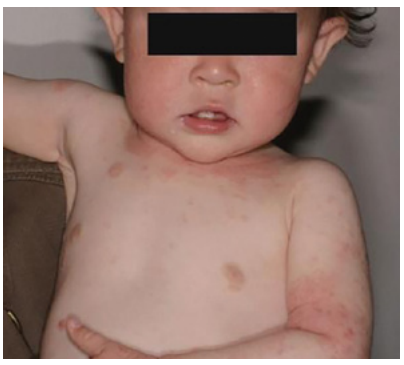

Figure 3 Atopic dermatitis in a young child (*courtesy of Danderm by Professor Niels K. Veien, Denmark*)

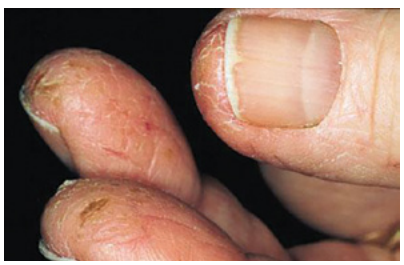

Figure 4 Protein contact dermatitis caused by garlic (*courtesy of Danderm by Professor Niels K. Veien, Denmark*)

Contact urticaria (CU) occurs due to contact between the offending food and the skin, most often face or hands. CU can be immunological (with sensitization) or non-immunological (without sensitization). CU is commonly seen as an occupational condition in patients handling food in their professional lives (e.g. bakers, chefs) or in children with atopic dermatitis.

MIXED IgE MEDIATED AND CELL MEDIATED CUTANEOUS MANIFESTATIONS OF FOOD ALLERGY

An association between childhood AD and FA has been demonstrated in numerous studies but the causal association between these often co-existing diseases is more controversial. Particularly infants/young children with AD (Figure 3) should be evaluated for FA; in a Danish birth cohort study 15% of young children with AD had a challenge verified FA and 90% of the children with FA had a concomitant diagnosis of AD. A more recent population-based cohort study of 4453 infants demonstrated that children with AD were 6 times more likely to have a FA at age 1 year compared with infants without AD. The likelihood of FA clearly increased with early debut of AD and the severity of the eczema. Importantly, also clinical irrelevant sensitization to foods are more common in children with AD, highlighting the need for thorough evaluation for FA including food challenges to avoid unnecessary dietary restrictions. Since late eczematous reactions to food without preceding immediate symptoms are not common, food challenges provide a valid tool for dietary guidance. An association between food allergy and atopic dermatitis in adults is uncommon.

Protein contact dermatitis (Figure 4) is characterized by a type I mediated immediate reaction of itching, erythema and/or urticaria following skin contact with high molecular food proteins. This immediate reaction is commonly followed by a delayed type IV eczematous reaction of a relapsing or chronic course.

CELL MEDIATED CUTANEOUS MANIFESTATIONS OF FOOD ALLERGY

Allergic, irritative, phototoxic/photoallergic and systemic contact dermatitis can rarely be caused by food hypersensitivity, but these conditions are beyond the scope of this short overview.

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8b FOOD-DEPENDENT EXERCISE-INDUCED URTICARIA AND ANAPHYLAXIS

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KEY MESSAGES

- Food-dependent exercise-induced anaphylaxis (FDEIA) is a anaphylactic reaction to a food occurring when food ingestion is combined with augmenting cofactors such as exercise
- The most common type is the WDEIA (wheat dependent exercise-induced anaphylaxis)
- Cofactors decrease the clinical threshold of allergen needed to elicit a reaction and increase severity

INTRODUCTION

Anaphylaxis is an acute life-threatening systemic or generalized hypersensitivity reaction involving the organs; skin, respiratory tract, gastrointestinal tract, and cardiovascular system. Exercise-induced anaphylaxis (EIA) is thought to be the cause of 5 - 15% of all cases of anaphylaxis. It can be assumed that the majority of patients with EIA suffer from food-dependent exercise-induced anaphylaxis (FDEIA). Food-dependent exercise-induced anaphylaxis (FDEIA) is a rare, but potentially severe food allergy exclusively occurring when food ingestion is accompanied by augmenting cofactors (Figure 1).

SYMPTOMATOLOGY AND ELICITORS

In most patients, FDEIA is initially clinically characterized by urticaria and angioedema, but in later episodes may progress to dyspnea, hypotension, collapse, and shock. Cases of death have been reported. FDEIA usually develops after ingestion of foods followed by physical exercise. The time between meal and exercise is usually between 30 - 120 minutes, but may be as long as about four hours. Other cofactors are nonsteroidal anti-inflammatory drugs, such as acetylsalicylic acid, alcohol, infections, stress, temperature extremes and menstruation. Various causative foods have been identified including shellfish, wheat, vegetables, fruits, and nuts. In middle and northern Europe as well as in Japan, wheat is the most common elicitor (wheat dependent exercise-induced anaphylaxis (WDEIA)). In Southern Europe food lipid transfer proteins have been assumed to be responsible.

MECHANISM AND DIAGNOSIS

The mechanisms of FDEIA remain unclear. Patients do react when allergen levels are high. Positive challenge results at peak or when the plateau plasma allergen levels are attained (Figure 2). Probably FDEIA is a sub-threshold food allergy, which requires cofactors for the elicitation. Cofactors decrease the clinical threshold of allergen needed to elicit a reaction and increase severity, although reactions also can be triggered at rest, when very high amounts of allergen are ingested (Figure 3). FDEIA presents an important and underdiagnosed diagnosis for emergency departments to consider. The prevalence is unknown, probably because of a lack of awareness. Exercise and other cofactors might increase gastrointestinal allergen permeability, osmolality, redistribute blood flow, or lower the threshold for IgE-mediated mast cell degranulation. Diagnostic tests for FDEIA are skin prick tests, *in vitro* food-specific serum IgE, and oral food provocation combined with subsequent exercise and other cofactors. Howev-

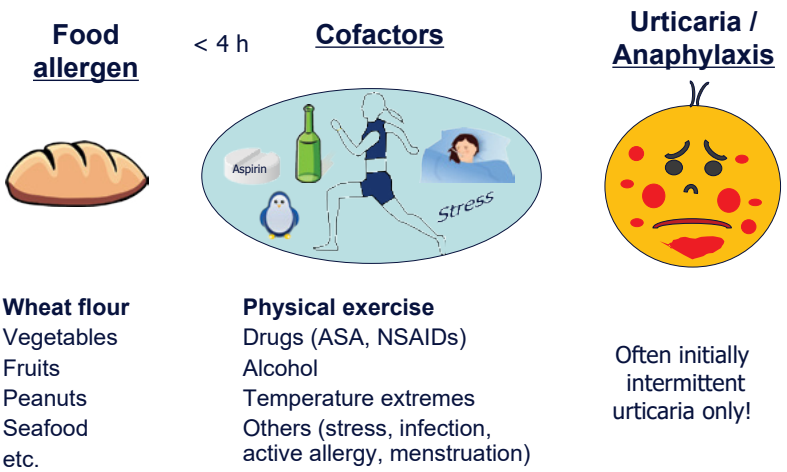

Figure 1 Principle of food-dependent exercise-induced anaphylaxis. Only in combination with the presence of cofactors, such as exercise, symptoms are elicited after intake of the food the patient is allergic to. Acute urticaria is the most frequent symptom, although depending on the amount of allergen ingested and the cofactors present, anaphylaxis is also common

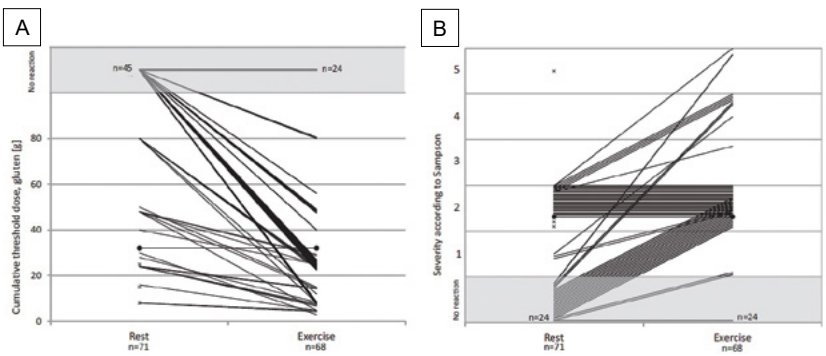

Figure 2 Exercise lowers threshold and increases severity in wheat-dependent exercise-induced anaphylaxis

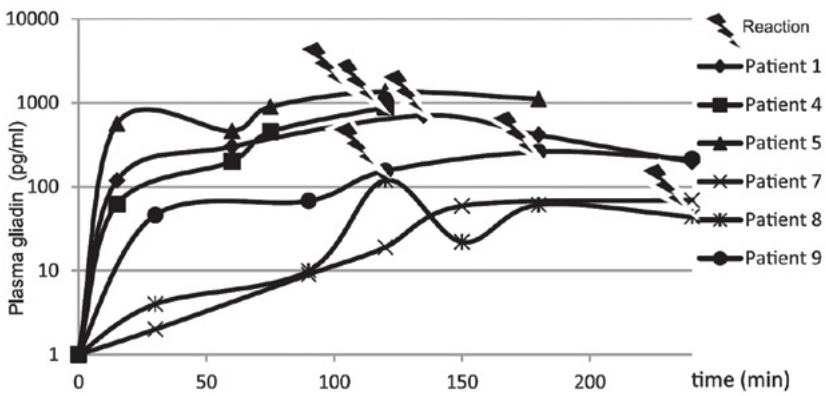

Figure 3 Plasma gliadin levels during challenges with gluten, with clinical thresholds indicated in patients with wheat-dependent exercise-induced anaphylaxis. Gliadin levels reached a peak at reactions to gluten plus cofactors

er, in WDEIA, SPT or IgE assays and even food provocation with wheat products and cofactors do not always show positive results; the best available tests are specific IgE to ω5-gliadin, as well as SPT to gluten and provocation with gluten plus cofactors.

THERAPY

The most reliable prophylaxis of WDEIA is a strict limitation of gluten ingestion before exercise. Refraining from exercise for four hours after wheat intake is a classical recommendation.

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9 EPIDERMAL SKIN BARRIER AND FOOD ALLERGY

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The skin provides a structural and immunologically active barrier between the internal and external environments that is essential for human life. This barrier forms a continuum with the epithelial lining of the gastrointestinal (GI) tract, but there are key differences in structure and function, such that potential allergens presented to the body through the skin may elicit a different response to those presented via the GI tract.

KEY MESSAGES

- Atopic dermatitis often precedes the development of food allergy, suggesting that skin barrier impairment plays a role in pathogenesis
- A mechanistic pathway from skin barrier defect to systemic IgE-mediated allergy has not been fully defined
- Structural and immunological mechanisms in epidermal keratinocytes may each contribute to the aetiology of food allergy
- Further research is needed to delineate a possible role for skin barrier enhancement as a strategy for primary and secondary prevention of food allergy, or treatment of established disease

EPIDEMIOLOGICAL AND ANIMAL STUDIES

Epidemiological studies show a strong association between atopic dermatitis (AD) and food allergy. However, it remains unclear to what extent the association results from the co-inheritance of genetic risk for atopic disease or whether there is a mechanistic pathway via skin barrier impairment. Animal models and early-life skin barrier assessment have been used to address this question. Epicutaneous exposure to food allergens stimulates a Th2-mediated immune response and anaphylaxis in mouse models. Skin barrier disruption and inflammation can also increase the severity of food allergic symptoms, even after the allergen has been removed. In the human context, a birth cohort study showed that skin barrier impairment (defined by transepidermal water loss in the upper quartile of distribution) measured soon after birth, predicts food allergy at 2 years of age.

GENETIC STUDIES

Genetic studies have added to the understanding of skin barrier function and food allergy (Table 1). The strongest association identified to date is between loss-of-function mutations in *FLG* and prevalence of peanut allergy. The level of environmental exposure to peanut allergen also increases risk of allergy, particularly in individuals with a *FLG*-null mutation. Deficiency of desmoglein 1 or corneodesmosin provide further evidence that IgE-mediated systemic allergy may arise from a structural epidermal abnormality. However it should be noted that genetic skin disorders with a greater degree of barrier impairment (*e.g.* epidermolysis bullosa) do not lead to an increased incidence of food allergy.

KERATINOCYTE-IMMUNE CROSSTALK

Sensitisation and allergy therefore appear to be controlled by specific molecular defects in the epidermal barrier and the crosstalk between keratinocytes and immune effector cells (Figure 1). Cytokines

TABLE 1

Genetic factors contributing to skin barrier function and associated with increased risk of food allergy

Gene, protein	Type of variant(s)	Evidence of association	References
Structural mechanisms			
FLG, filaggrin	Loss of function mutations	Associated with peanut allergy (not dependent on AD) OR~1.9-5.3	Brown et al. J Allergy Clin Immunol 2011; 127: 661-667
	SNVs	GWAS for food allergy	Marenholz et al. Nat Comm 2017; 20;8:1056
SPINK5, serine protease inhibitor Kazal type 5	Loss of function mutations (autosomal recessive)	Food allergy is one feature of Netherton's syndrome	Chavanas et al. Nat Genet 2000; 25:141-2.
	SNV which may reduce gene expression	Associated with challenge-proven food allergy OR~1.65 from meta-analysis	Ashley et al. Allergy. 2017; 72:1356-1364
CDSN, corneodesmosin	Loss of function mutations (autosomal recessive)	Skin peeling syndrome can be associated with food allergy	Oji et al. Am J Hum Genet 2010; 87:274-281
DSG1, desmoglein 1	Homozygous mutations	Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting	Samuelov et al. Nature Genetics 2013; 45:1244–1248
Immunological and/or possible structural mechanisms			
SERPINB cluster, *clade B serpin*	SNVs in gene cluster	GWAS for food allergy; the serpins may contribute to an immunological and/or structural barrier defect	Marenholz et al. Nat Comm 2017; 20;8:1056
EMSY, EMSY or *LRRC32*, leucine-rich repeat-containing 32	Intergenic SNVs	GWAS meta-analysis for food allergy; this locus may represent an immunological or structural barrier defect	Asai et al. J Allergy Clin Immunol 2018; 141: 991-1001 Marenholz et al. Nat Comm 2017; 20;8:1056
HLA-DR and DQ	MHC locus	GWAS and meta-analysis for peanut allergy	Hong et al. Nat Comm 2015; 24;6:6304 Asai et al. J Allergy Clin Immunol, 2018; 141:991-1001 Marenholz et al. Nat Comm 2017; 20;8:1056

OR, odds ratio; SNV, single nucleotide variant; GWAS, genome-wide association study

produced by keratinocytes, including IL-33, IL-25 and TSLP, may contribute to the observed progression from AD to food allergy and transcriptome analysis of the stratum corneum has shown that patients with AD and food allergy have an 'immature' skin barrier and evidence of immune activation, even on clinically normal skin.

FUTURE PROSPECTS

Early intensive emollient therapy in high-risk infants reduces the incidence of AD by ~50% and may also reduce food sensitisation, but larger studies are on-going to clarify this finding. There is also preliminary evidence that epicutaneous immunotherapy may be an effective treatment for established food allergy. An increased understanding of the role of skin barrier impairment in systemic allergy may, in the future, offer important opportunities for primary and secondary prevention.

ACKNOWLEDGEMENTS

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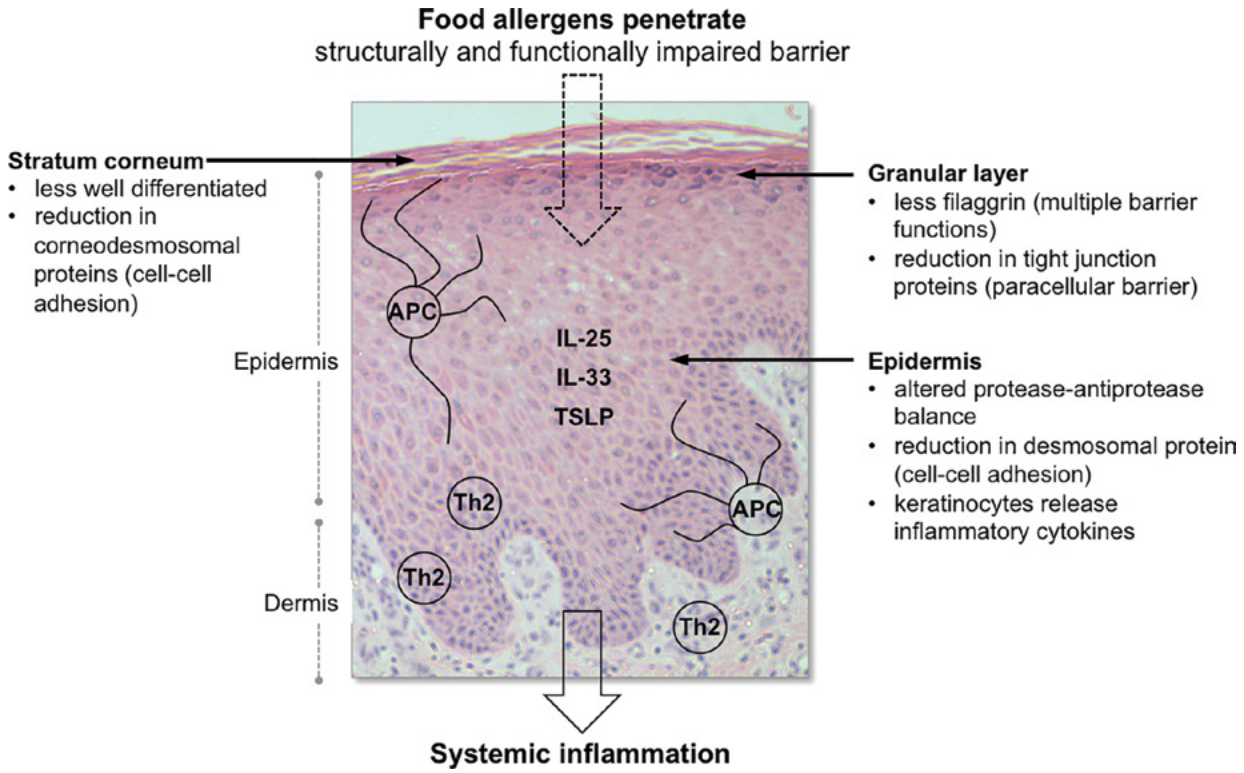

Figure 1 Histological section of human skin showing structural and immunological mechanisms in the epidermis contributing to the pathogenesis of food allergy. APC, antigen presenting cell; IL, interleukin; Th2, T-helper cell; TSLP, thymic stromal lymphopoietin; dermal cells contributing to atopic inflammation are not represented

matological Research Charity; skin histology in Figure 1 is used courtesy of the Tayside Bioresource.

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Section F

SKIN ALLERGY RESEARCH MODELS

* Animal models of skin allergy
* Animal models for skin barrier dysfunction
* In vitro or ex vivo models of skin allergy
* Microdialysis

1a ANIMAL MODELS OF SKIN ALLERGY

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KEY MESSAGES

- Animals with specific genetic backgrounds, housed under defined conditions, serve as valuable models to mimic human conditions
- Animal models enable examination of immunologic, cellular or molecular pathways of allergic diseases and can provide new insights in the pathogenesis of allergy and tolerance
- Animal models allow proof of concept studies for development of novel therapies
- Translation of data obtained in animal models to humans needs be done with care, as the immune responses in animals do not always exactly reflect the human situation

Animal models can be used to mimic human *in vivo* situations under controlled experimental conditions. Their special strength is that the role of individual genes can be assessed in genetically modified mouse strains. Animal models are useful to study the pathophysiology of skin allergy, such as epidermal barrier function, cellular- and molecular pathways of skin immunology, effect of environmental factors on the skin, gene expression studies or drug discovery and safety (Table 1).

With current technologies, knockout models and transgenic mice can be designed almost for every gene of interest. To study epidermal barrier dysfunction a wide range of models are available, such as the use of hairless mice, filaggrin or keratin deficient mice. Tape stripping of the skin is used to induce barrier disruption to study sensitization or gene expression. Humanized murine models are relevant to study IgE mediated allergies. A patch test is a useful tool to investigate contact dermatitis. Transgenic mice expressing epidermal self-antigens under Keratin promoters are used to study of immune responses to skin associated antigens. Besides, oral sensitization, intradermal injection or epicutaneous antigen sensitization are used to study food allergy. Topical applications also serve as provocation route for investigation in food allergies. Figure 1 shows frequently used skin applications. For skin allergy studies, murine models are frequently used, but also dogs or pigs can be used as animal models.

The genetic background of the animal affects immune responses. So are C57BL/6 and BALB/c Th1- and Th2-type prone mouse strains, respectively. Thus, it is important to choose the most correct model to answer the research question. Data are considered to be stronger when the results can be confirmed using another model. The interpretation of data obtained in animal models requires careful considerations when translated to human beings as the immune responses in animals are not entirely the same as in humans. Finally, findings from animal models need to be confirmed using human *in vitro* and *in vivo* studies, including validation of therapeutic options in clinical trials.

Domestic animals (including dogs, cats and horses) also spontaneously develop allergies, but far less is known about the development of allergy in animals. Comparison of spontaneous allergies in humans and animals may give new insights into exposure to allergens

TABLE 1

Overview of experimental animal models to study skin allergy

	Atopic dermatitis	Allergic contact dermatitis	Autoimmunity in allergy	Food Allergy	Itch	Skin inflammation	Drug discovery
Animal model	BALB/c, C57BL6 mice NC/NgaTnd mice Transgenic mice Knockout mice Beagle dogs	C57BL6 mice Knockout mice Transgenic mice Hairless mice 129/Sv mice	C57BL6 mice Transgenic mice	BALB/c, C3H/HeJ, C57/BL6 mice Humanized mice Rats Spaniel/basenji or beagle dogs Pigs (swine)	C57BL/6 mice Transgenic mice Knockout mice NC/NgaTnd mice Beagle dogs	BALB/c mice Knockout mice Transgenic mice Humanized mice SCID mice 129/Sv mice	BALB/c mice Knockout mice Humanized mice 129/Sv mice Hairless mice
Method	Topical application Hapten exposure Histology/IHC Blood/serum Scratching behaviour SPF conditions	Patch test Topical application Scratching behaviour SPF conditions	Histology/IHC T cell proliferation Peripheral blood Adoptive transfer of T cells Tape stripping	Patch test Topical application MC903 treatment Histology Tape stripping SPF conditions Anaphylaxis scores	Video recording Scratching behavior Wiping Calcium-imaging Histology/IHC IL-31 administration	Histology/IHC MC degranulation Skin allograft model Patch test Skin swabs	Histology/ICH Topical application EPIT/SCIT Nanoparticles Photo documentation
Read-out	Morphology Th1/Th17/Th22 Th2 cytokines Total/specific IgE Skin eosinophils Skin barrier TEWL Filaggrin expression Itch/IL-31 expression Response to corticoids STAT pathway IgE/IgG levels	Skin DC migration Skin eosinophils + neutrophils IgE levels Toll like receptor IL-1β, IL-6, IL-4, IL-20, IL-19, IL-22, IL-24, IL-33, TSLP, TNF Ear thickness	Morphology Autoreactive IgE Autoreactive IgG Cytokine levels (IL-15) STAT pathway CD4+/CD8+ T cells IFNγ levels OVA mRNA expression	Body temperature Diarrhea Ear thickness Th2 cytokines IL-10, TGFβ , IFNγ Specific IgE, IgG1, IgG2a, IgA Expansion of MCs Serum mMCP Number of Tregs, Th1 and Th2 cells Skin eosinophils	Itch IL-31 levels TRPV4 expression 5-HT signaling Calcium potentials Neuropeptides Morphology Inflammatory cells Total serum IgE TEWL	Morphology Skin eosinophils Inflammatory cells IL-1α + Th2 cytokines Total serum IgE Cell proliferation Expression of keratins Tryptase CLA expression Microbiome	Efficacy Safety Morphology Skin barrier function Cytokine levels MC degranulation Inflammatory cells Ear thickness Itch Serum IgE

Abbreviations: CLA: Cutaneous lymphocyte antigen; DC: Dendritic cells; EPIT: epicutaneous immunotherapy; IFN: Interferon; IHC: Immunohistochemistry; MC: mast cells; MMCP: Mucosal mast cell protease; SPF: Specific-pathogen-free; SCIT: subcutaneous immunotherapy; TEWL: Trans-epidermal water loss; Th2: T helper 2 lymphocytes; TNF: Tumor necrosis factor; Tregs: T regulatory cells; TRPV: Transient Receptor Potential Vanilloid; TSLP: Thymic stromal lymphopoietin; 5-HT: 5-Hydroxytryptamine

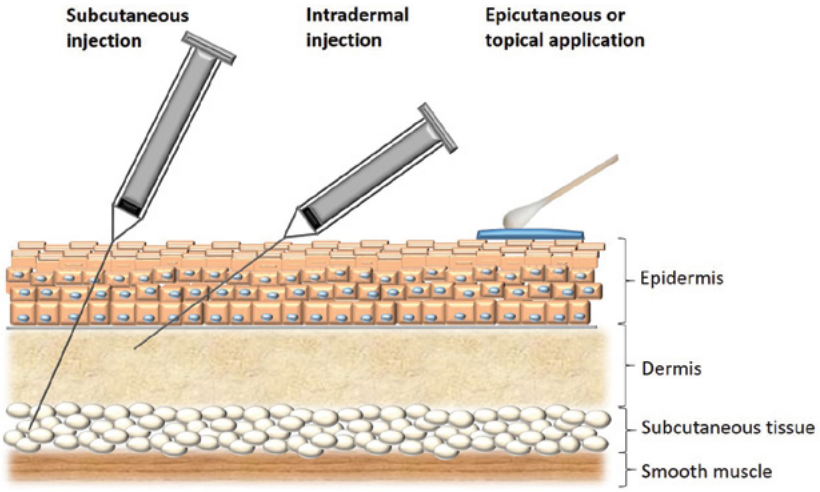

Figure 1 Skin application techniques. Frequently used injection or application techniques to study skin allergy

and the influence of the environment or genetic background on the development of allergy.

Other experimental approaches may replace the use of animals to study the human pathophysiology, such as human skin equivalents and *in silico* computational models, which are mathematical analyses that can predict disease prognosis or responses to treatments. Although all models can provide novel insights in allergic skin diseases, clinical trials in patients are needed to study safety and efficacy in human beings.

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1b ANIMAL MODELS FOR SKIN BARRIER DYSFUNCTION

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KEY MESSAGES

- Primary skin barrier dysfunction is a key pathological feature for the initiation of a pathological skin inflammation
- Animal models with primary skin barrier dysfunction help to reveal the mechanistic link between skin barrier properties and cutaneous inflammation
- The selection of genetically modified animal models together with an appropriate treatment scheme must be done carefully relating to the respective research issue

Epidemiologic and genetic evidence have suggested primary skin barrier dysfunction as key pathological feature for the initiation of skin inflammation and a facilitated percutaneous antigen-sensitization and thus for mounting allergic diseases, such as atopic dermatitis (AD) and the further development of asthma, food allergies, and allergic rhinitis (Figure 1).

Several animal models with primary skin barrier dysfunction have been developed to understand the role of these candidate genes not only for biophysical properties of the skin, but also to elucidate the mechanistic link between skin barrier defects and increased risk of atopic diseases (Table 1).

Loss-of-function mutations in the gene encoding the epidermal protein filaggrin are recognized as the strongest genetic risk factor for AD, but also for AD-associated asthma. Filaggrin and its metabolites are key components for maintaining normal skin barrier function and skin barrier impairment due to filaggrin mutations is caused by factors such as reduced amounts of natural moisturizing factor (NMF) in the *stratum corneum*, loss of corneocyte integrity and impairment of *stratum corneum* cohesion. Filaggrin-deficient mice showing either a frameshift mutation in the filaggrin gene ($Flg^{ft/ft}$) or bearing a loss-of-function mutation ($Flg^{-/-}$) are available to study the absence of filaggrin. As depicted in Figure 2, a mouse model with a combined loss of filaggrin and hornerin ($FlgHrnr^{-/-}$) mirrors two high susceptibility loci for AD and nicely reflects a subclinical phenotype seen in humans. Further, mutations within genes involved in the degradation process of profilaggrin are of high importance to clarify the multimodal impact of filaggrin degradation products in the formation and maintenance of skin barrier and the further cutaneous inflammation (Table 1, FLG metabolism).

Besides, other genes of the epidermal differentiation complex on the human chromosome 1q21 contribute to skin barrier formation and have been linked to AD, e.g. filaggrin-like proteins such as filaggrin-2 or hornerin, which are presumed to have similar functions as filaggrin or other structural/scaffold proteins of the cornified envelope (Table 1). Further, mechanisms which are involved in corneocyte desquamation (e.g. proteases, protease inhibitors or corneodesmosomal proteins), the synthesis of intercellular lipid lamellae, the production of anti-microbial defense, or the formation of tight junctions (Table 1) were shown to be associated with decreased barrier function and/or AD, asthma, and elevated serum IgE.

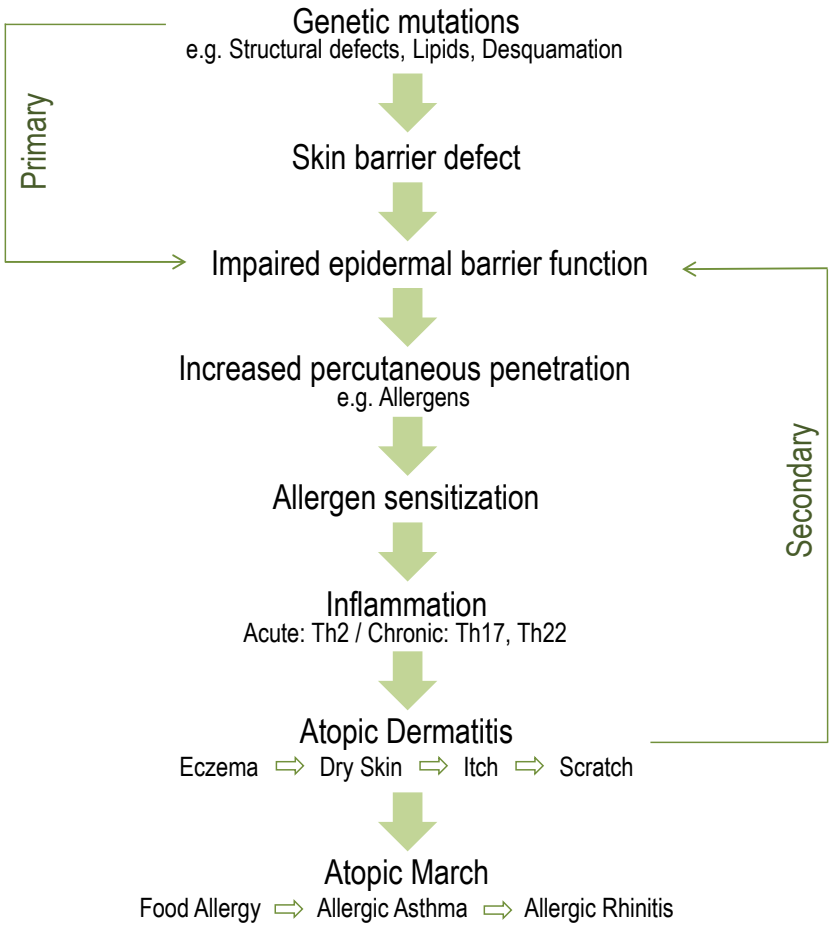

Figure 1 Consequences of primary skin barrier defects on the development of allergic diseases.Genetic mutations that cause primary skin barrier defects with an impaired epidermal barrier function lead to an increased penetration of foreign substances (e.g. allergens) and a facilitated percutaneous allergic sensitization. The induced acute Th2-skewed inflammatory reaction leads to the symptoms of atopic dermatits with eczema, dry skin, itch and scratching, which further promotes a secondary skin barrier impairment and triggers additional chronic inflammation. As a consequence, this promotes the development of other allergic disorders, e.g. food allergy, allergic asthma, and allergic rhinits within the progression of the atopic march

It is important to consider that variances, such as age and genetic background of mouse models might have implications on skin barrier status and immunological outcome. For example, hair growth seems to compensate epidermal barrier abnormalities, thus neonatal or hairless mice might be superior for certain aspects, e.g. skin barrier properties. Further, using C57BL/6 or BALB/c background induces a Th1- or Th2-deviated immune response, which might be important for immunological outcomes.

Together, mouse models with genetic defects targeting the epidermal barrier function are of great interest, since they mimic human disease very closely. Depending on the research question, all the mentioned mouse models with primary skin barrier deficiencies can be used in models to study the immunological processes of different diseases, e.g. AD, food allergy, allergic asthma, or contact dermatitis using an adequate treatment scheme.

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TABLE 1

Genes involved in primary skin barrier formation [based on references 1, 6-8].

Function	Gene name	Gene symbol
Terminal epithelial differentiation		
FLG metabolism	Filaggrin	*FLG*
	SASpase	*ASPRV1*
	Caspase14	*CASP14*
	Caplain	*Caplain1*
	Bleomycin hydrolase	*BLMH*
Filaggrin-like proteins	Filaggrin2	*FLG-2*
	Hornerin	*HRNR*
Cornified envelope formation	Involucrin	*IVL*
	Loricrin	*LOR*
	Envoplakin	*EVPL*
	Periplakin	*PPL*
	Small proline-rich protein	*SPRR*
	Transglutaminase1/3/5	*TGM1/3/5*
Cytoskeleton	Keratin1/10	*KRT1/10*
Corneocyte desquamation		
Proteases	Kallikrein5/7/14	*KLK5/7/14*
	Protease-activated receptor 2	*PAR2*
	Cathepsin	*CTSB*
	Caspase14	*CASP14*
Protease inhibitors	Lympho-epithelial Kazal-type-related inhibitor (LEKTI)	*SPINK5*
Structure of corneodesmosome	Desmoglein 1	*DSG1*
	Desmocollin 1	*DCN1*
	Plakophillin	*PKP*
	Corneodesmosin	*CDSN*
Composition of intercellular lipid lamellae		
Lipid synthesis	12R-lipoxygenase	*ALOX12B*
	Lipoxygenase 3	*ALOX3E*
Transmembranal transport of lamellar bodies	ATP-binding casstee subfamily A member 12	*ABCA12*
	Transmembrane protein 79/mattrin	*Tmem79/Matt*
Antimicrobial peptides (AMP)		
Immune barrier	Cathelicidin	*Cramp*
	ß-defensin	*HBD-2/-3*
Formation of tight junctions		
Cohesion in the *stratum granulosum*	Claudin	*CLDN1*
	Occludin	*OCLN*

Figure 2 Detailed phenotype of 4-days-old *FlgHrnr*$^{-/-}$ mice with macroscopic appearance and characteristic features (adapted from Rahrig et al. 2019 [5]).

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2 *IN VITRO* OR *EX VIVO* MODELS OF SKIN ALLERGY

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KEY MESSAGES

- There is a great potential for clinical use of *in vitro*, *ex vivo* and *in vivo* models in skin allergies, i.e. their diagnosis and assessment of therapeutic agents
- Various *in vitro* approaches exist to mimic certain pathophysiological aspects of skin allergies
- *In vitro* human skin reconstructs are an important tool to study tissue responses in the epidermis in general and skin barrier function in skin allergy

The term skin allergy designates immunological hypersensitivity reactions ranging from allergic drug reactions, allergic contact dermatitis (ACD), urticaria and angioedema to atopic dermatitis (AD). The use of *in vivo* (animal) models have considerably contributed to a better understanding of skin allergies, however there is considerable interest to decrease the *in vivo* experiments in skin research by giving more emphasis on *in vitro* and *ex vivo* models.

Beyond animal experiments, a number of *in vitro* approaches have been developed. *In vitro* models are, besides their use in studying skin barrier and keratinocyte biology increasingly attractive for diagnostic purposes and for the assessment of therapeutic compounds. Disease-relevant features are explored in patient-derived leukocytic/non-leukocytic cells or in skin equivalents.

Among *in vitro* approaches, human skin reconstructs may be the most important and promising one (Figure 1). They allow to study barrier function and keratinocytes biology and the reaction following exposure to environmental agents, allergens and drugs. In some models, keratinocytes are seeded on a porous membrane or a fibroblast-populated dermal matrix. More complex approaches incorporate immune cells such as Langerhans cells in the model. One of the most recent advances is the "skin-on-a-chip", a skin model in a perfusable microphysiological culture system, thus accounting for the dynamic components of the cutaneous barrier (microbes and immune cells). In AD, human skin reconstructs mimic epidermal barrier dysfunction, a key pathogenic feature. In ACD, skin explant models represent precious tools to study the penetration of haptens and their sensitizing potential. In both situations, the effect of potential therapeutic agents can be assessed.

As to systems using patient-derived (immune) cells to reproduce certain disease mechanisms, their relevance is illustrated by the example of allergic drug reactions: the so-called lymphocyte transformation test as an example measures the proliferative response of patient-derived T cells after drug exposure and is used as a diagnostic tool. Taken together, *in vivo* and *in vitro* models of skin allergies offer a wide range of tools not only allowing to study molecular and cellular mechanistic aspects in the pathophysiology, but having a use in diagnostics and the assessment of therapeutic agents.

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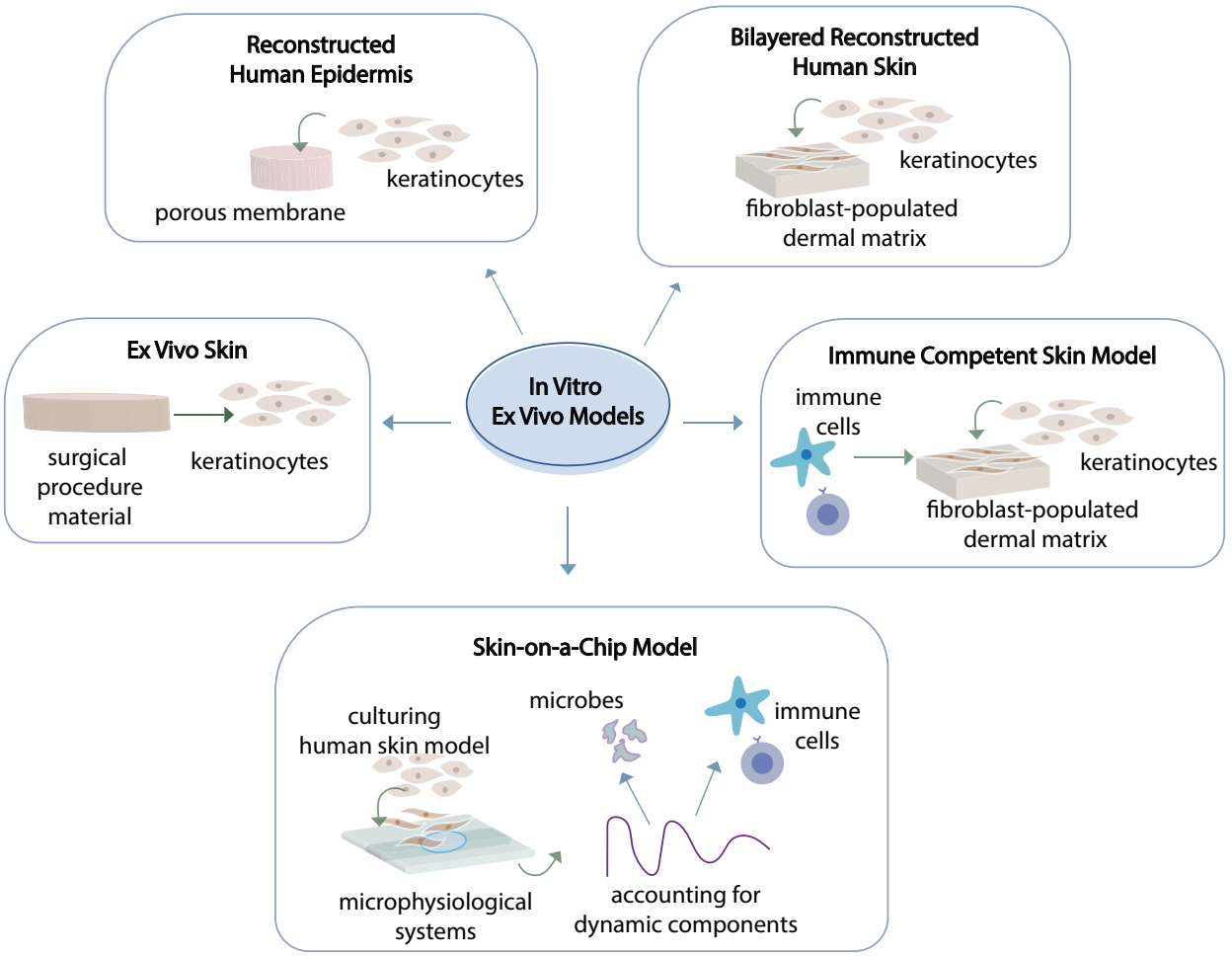

Figure 1 Schemes of reconstructed human skin models. From the left to the right: Ex vivo skin: Freshly obtained skin (from surgical procedures). Reconstructed Human Epidermis: Keratinocytes seeded onto a porous membrane. Simplest organotypic skin model with epidermal barrier function. Bilayered Reconstructed Human Skin: Keratinocytes seeded on a fibroblast-populated dermal matrix. Immune Competent Skin Models: Reconstructed Human Epidermis or Bilayered Reconstructed Human Skin incorporating immune cells (e.g. Langerhans cells, T lymphocytes). Allows studies on immune cells in the barrier setting. Skin-on-a-Chip: Culturing human skin models in microphysiological systems. Accounts for dynamic components

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3 MICRODIALYSIS

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KEY MESSAGES

- Dermal microdialysis recovers water soluble mediators from the skin
- It may be used to study the mechanisms of allergy and urticaria
- It may also be used to look at the effects of treatment
- Samples may be collected continuously for up to 24 hours
- Unlike biopsy dermal microdialysis leaves no scarring

How do the cells of the skin talk to each other? Are the messages they send different in health and disease? How can we find out? We can use skin microdialysis, which is a versatile sampling technique that recovers soluble endogenous and exogenous molecules from the extracellular compartment of human or animal skin. To perform skin microdialysis, thin tubular dialysis membranes are inserted into the dermis or the subcutis and perfused at a low speed with a physiological solution (Figure 1). Endogenous or exogenous molecules soluble in the extracellular fluid diffuse into the tubular microdialysis membrane and are collected in small vials for analysis. The duration and timing of the collected dialysate samples allows kinetic evaluation of the events occurring in the tissue. A comprehensive review on skin microdialysis has been published recently.

One of the early skin microdialysis studies investigated the mechanism of the early phase response in human skin by insertion of microdialysis probes into different areas of the allergen-induced wheal and flare response (Figure 2). The results showed that histamine was released in the wheal but not the flare. Further studies have shown that the neurogenic flare is mediated primarily by calcitonin gene related peptide (CGRP). In a subsequent study, the cytokine response to dermal allergen provocation was studied over a period of six hours. The results showed that the cytokine profile of every person studied was different illustrating the ability of skin microdialysis to unravel the complexities of dermal allergic responses.

In addition to Type 1 hypersensitivity, skin microdialysis is now being used to explore the mechanisms of other dermal conditions, including urticaria, atopic dermatitis, psoriasis, dermal pain, drug hypersensitivity and ultraviolet B-induced skin responses. In addition for the search for biomarkers, the effects of drug treatment on the mediator and cytokine mechanisms of these conditions can be explored in detail. Inducible forms of urticaria, such as cold urticaria, where responses may be induced over the site of probe insertion, are particularly suitable for skin microdialysis study. In addition to exploring disease mechanisms and treatment effects, skin microdialysis has been used to study the accumulation and metabolism of drugs in the dermis after both local and systemic administration.

In conclusion, skin microdialysis is a valuable tool for research in dermatological allergology and beyond, and awareness of and further improvements in skin microdialysis will increase its use and utility in experimental and clinical studies.

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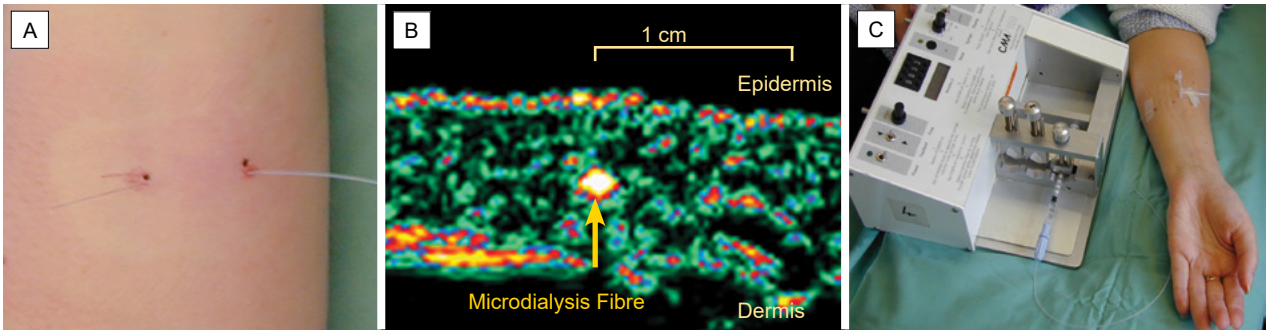

Figure 1 Skin microdialysis: probe insertion and pump unit. A. a microdialysis probe inserted into the volar forearm for a distance of 2 cm at a depth of approximately 0.2 – 0.3 mm. B. Probe depth. C. Microdialysis pump delivering perfusate at a rate of o.1 to 0.5 microlitres per minute. On the right is a small perfusate collection vessel

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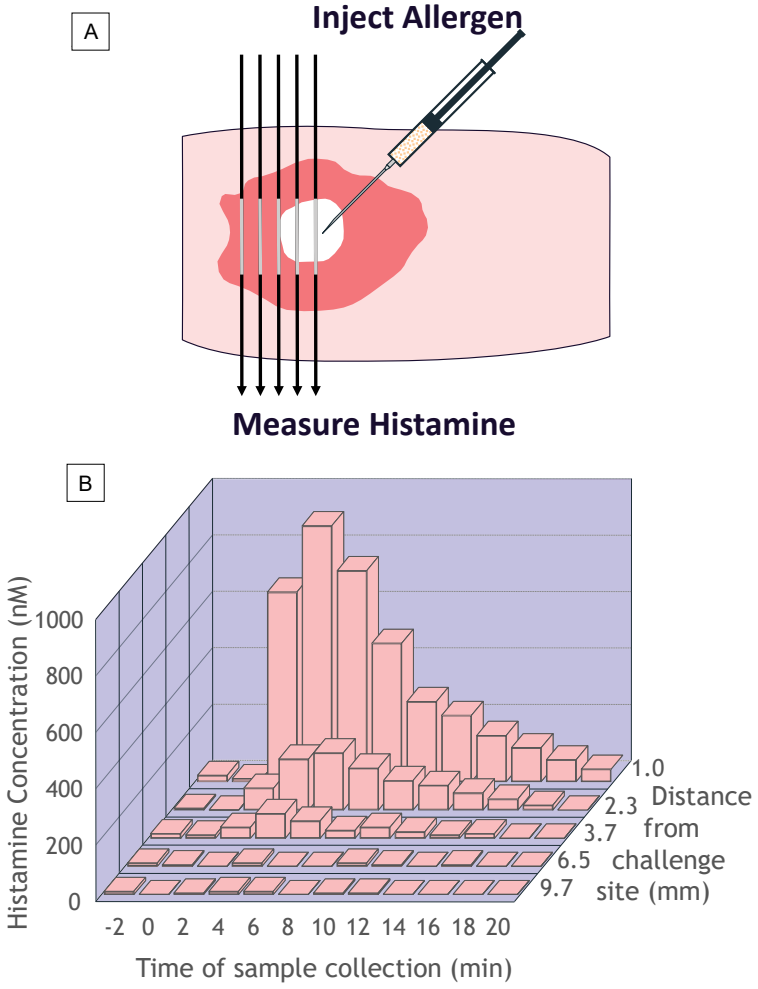

Figure 2 Release and diffusion of histamine in the allergen induced wheal and flare response. A. Positioning of the microdialysis probes to collect histamine. The wheal diameter in this experiment was 5 mm. B. the concentration of histamine recovered from the probes positioned at the stated distance from the allergen injection site. Note that there was no histamine recovered outside the wheal area. Data is from reference 2

Section G

QUALITY OF LIFE IN PATIENTS WITH SKIN ALLERGIES

* Quality of life in patients with skin allergies

1 QUALITY OF LIFE IN PATIENTS WITH SKIN ALLERGIES

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KEY MESSAGES

- Allergic diseases of the skin such as atopic dermatitis, urticaria or hand eczema have a quality of life impact that is similar to other chronic conditions such as diabetes
- Generic, dermatology and disease specific instruments exist to measure the quality of life impact of allergic diseases of the skin
- When measuring QoL in allergic diseases of the skin one needs to be sensitive to issues arising from measurements being done in children vs parents and when translating questionnaires into other languages

Allergic skin disorders may have little impact on life expectancy (**quantity of life**) but can have a major impact on its **quality**. A person with an allergic skin disease may have both physical and psychological consequences of their disease, for example the itching and visible signs of their atopic eczema may be accompanied by embarassment, worry and even depression. The need for a holistic approach and the measurement of the outcomes important to the patient are essential. Patient reported outcome measures were first developed for clinical trials and epidemiological studies, but are now also used in clinical practice to assess and track disease severity from the patients' point of view, monitor response to treatment or justify the prescription of an expensive drug. Health-related quality of life (HRQOL, the aspects of quality of life which are affected by health status) is one of the most important patient-reported outcomes, complementing the objective assessment of disease severity. In patients with skin allergy, HRQOL can be measured by generic instruments such as the EuroQoL (EQ) – 5D which allow for comparability across diseases, or by dermatology specific instruments such as the Dermatology Life Quality Index (DLQI) which enables comparison across different skin diseases. There is also a third type of measure, disease-specific instruments (such as the Chronic Urticaria Quality of Life Questionnaire (CU-QOL) or the Quality of Life in Hand Eczema Questionnaire (QOLHEQ)), these are particularly favoured in the clinical trial setting because they are more sensitive to change.

Allergic skin diseases can have a large impact on people's HRQOL. One large study investigated HRQOL in 4010 patients with skin disease and 1359 controls across 13 European countries. People were asked to rate their health on the EuroQoL visual analogue scale, which ranges from 0 (worst) to 100 (best imaginable health state) and values for atopic dermatitis, urticaria, hand eczema and eczema were less than 70 as opposed to 82 for controls (Figure 1) and 69 for diabetes, a value referenced by Balieva et al. from a UK study. The inverse association of the four dermatological disease entities with self-rated health remained significant even after adjusting for age, sex, socioeconomic status and comorbidities. Patients and controls also completed the other components of the EQ 5 D which assesses health status in the five dimensions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Significant impairments were found in all of these dimensions except mobility

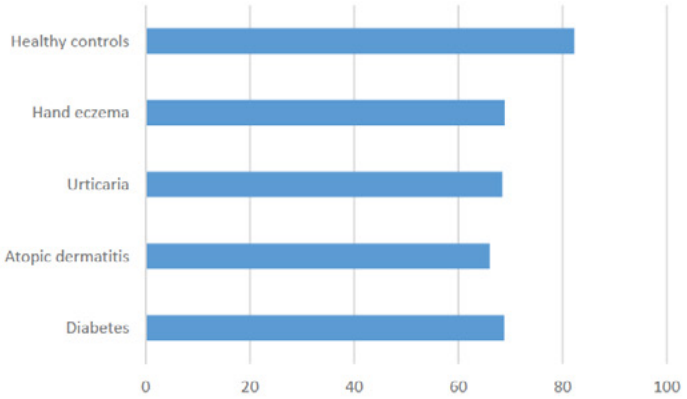

Figure 1 EuroQoL VAS scores as reported/referenced by Balieva et al. 2017

TABLE 1

Selection of HRQOL instruments (generic, dermatology-specific, disease-specific)

Instrument	Target population	Recall period	Number of items
EuroQoL (EQ) 5 D *Brooks 1996 Health Policy*	Wide range of diseases	On the day	5
Dermatology Life Quality Index (DLQI) *Finlay & Kahn 1994 BJD*	Adults with skin disease	One week	10
Skindex *Chren et al. 1996 J Invest Dermatol* *Chren et al. 2001 J Cutan Med Surg* *Nijsten et al. 2006 J Invest Dermatol*	Adults with skin disease	One week	29/ 16/ 17
Quality of Life in Hand Eczema Questionnaire (QOLHEQ) *Ofenloch et al. 2014 BJD*	Adults with with hand eczema	One week	30
Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) *Baiardini et al. 2005 Allergy*	Adults with chronic urticaria	Two weeks	23

for atopic dermatitis and hand eczema, and in pain/discomfort and anxiety/depression for urticaria. The findings of this multinational multi-disease study corroborate previous findings from studies conducted in atopic eczema and hand eczema which also showed impaired generic HRQOL in comparison to controls.

Many different instruments exist to measure HRQOL in people with skin allergies. Ideally, whether for use in research or clinical practice, one wishes to use instruments that have been tested for validity and reliability and have adequate measurement properties, are feasible to administer in the respective setting and produce scores which are interpretable. Systematic reviews of the quality of HRQOL instruments are helpful to guide

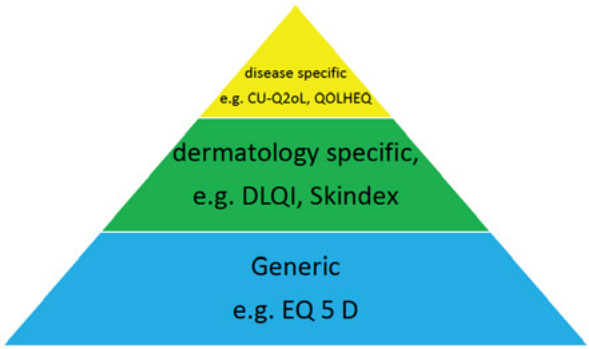

Figure 2 Pyramid of HRQOL instruments (generic, dermatology-specific, disease-specific)

the choice of instruments, but the evidence base is often insufficient. For instance, a recent systematic review assessing over 100 measurement properties of HRQOL instruments available for children and adults with atopic eczema concluded that for most measures no recommendation can be given for their use without the conduct of more validation studies. Table 1 shows a selection of instruments available for a wide range of diseases, skin diseases in general, as well as hand eczema and chronic urticaria more specifically.

HRQOL measures are often used in multinational studies but one needs to be cautious when translating HRQOL questionnaires as it cannot be assumed that they remain valid in the target population. Assessing relevance, comprehensiveness and comprehensibility through patient interviews is important and will yield linguistically valid versions of a given HRQOL measure. Still, questionnaire items may function differently across cultures but statistical methods are available to adjust the scorings in order to achieve comparability.

As allergies frequently occur in childhood, it is important to think about the quality of life impact of allergic diseases on children and their family (parents and siblings). A pragmatic approach is to obtain data on HRQOL from parents as proxies but instruments have also been developed for direct measurement in children from school age (5/6 years) onwards and for adolescents. HRQOL data obtained from parents and children may not always be congruent.

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Section H

MANAGEMENT OF ALLERGIC SKIN DISEASES

* General principles of topical therapy of the skin
* Topical corticosteroids
* Calcineurin inhibitors
* Proactive therapy of atopic dermatitis
* Wet wrap therapy
* Allergen immunotherapy principles and mode of action
* Allergen Immunotherapy: Subcutaneous (SCIT) and sublingual routes (SLIT)
* Epicutaneous immunotherapy
* Educational programs for skin allergy

1 GENERAL PRINCIPLES OF TOPICAL THERAPY OF THE SKIN

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PARTICULARITY OF TOPICAL THERAPY

Topical therapies offer the unique advantage that **products** (Figure 1) for treatment are applied directly to the affected skin resulting in a local, prolonged and intimate contact of product and skin. Therefore, **ingredients** forming the **vehicle** play a crucial role in the absorption of actives. They are able to transiently decrease the skin barrier function by various mechanisms. Some active-free vehicles show substantial clinical effects. E.g., commonly used vehicle ingredients (petrolatum, glycerin, dimethicone) have demonstrated efficacy in skin barrier repair and symptom relief in steroid-responsive conditions. Hence, vehicle ingredients of topical products may evolve **intrinsic effects** that may be clinically substantial.

VEHICLE TERMINOLOGIES

A rich vocabulary used by regulatory bodies, industry, scientists, healthcare professionals, patients and consumers has evolved to describe the vehicle of topical products. **Vehicle formats** are often associated with the conveyance of specific effects (Figure 2).

KEY MESSAGES

- Topical therapies offer the unique advantage that products are applied directly to the affected skin resulting in a local, prolonged and intimate contact of product and skin
- The vehicle choice is based on the nature of the dermatosis (size, location and skin condition)
- Vehicle polarity (hydrophilic vehicles on hydrophilic skin, lipophilic vehicles on dry skin) and vehicle viscosity (low viscosity on large and high viscosity on small skin areas) lead to an optimal contact between vehicle and affected skin and allow an uncomplicated application and distribution
- A realistic application quantity is rarely more than 5 mg/cm^2. For semi-solid vehicles, the Finger Tip Unit (400-500mg) and for more liquid vehicles mechanical dosage aids (e.g., pump with weight data per pump stroke) both with dosing tables/ instructions are recommended

METAMORPHOSIS OF THE VEHICLE

The format of topical products containing volatile vehicle ingredients may change dramatically after application onto the skin (Figure 3a, 3b). It becomes obvious that vehicles on the skin after application may be very different from vehicles in their primary container. Conclusions referring to effects originating from the vehicle format in the primary container are not possible. The paradigm – often disseminated for topical corticosteroids – that ointments are more potent than creams and creams are more potent than lotions is not valid.

VEHICLE CHOICE

Adjusted vehicle **polarity** and **viscosity** lead to an optimal contact between vehicle and affected skin and allow an uncomplicated application and distribution on the skin (Figure 4).

PRACTICAL ASPECTS

To avoid treatment failures, explicit instructions on quantity to be applied per area and time should be given. This requires that areas of

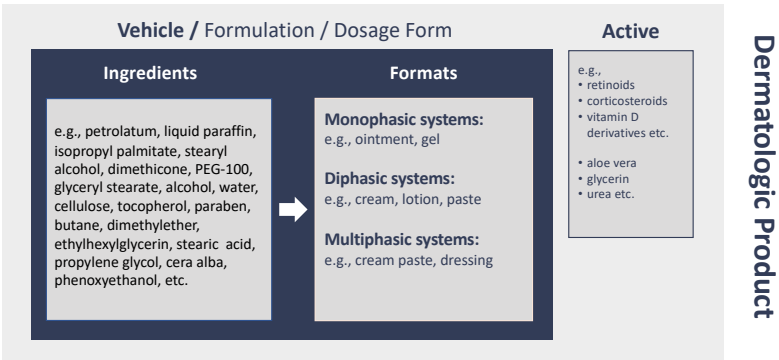

Figure 1 Topical dermatologic products are typically comprised of an active and a vehicle ranging widely in their physicochemical and textural nature. They are applied to diverse body surfaces of different properties (wet/dry, mucous/non-mucous, healthy/diseased) and size. The nature of the vehicle should be adapted to the nature of the skin to be treated to optimize application and contact of product with skin (Figure 4). All vehicles are made of vehicle ingredients. Depending on their physicochemical nature and the manufacturing process a three-dimensional structural matrix or typical vehicle format evolves, e.g., monophasic (ointment), biphasic (cream) or tri-/multi-phasic systems (cream paste). For all formats both lipophilic and hydrophilc forms exist. Some formats are defined in pharmacopoeias - note that differences between pharmacopoeias exist (1, 2). The vehicle has the task of keeping an active stable and making it bioavailable, i.e. releasing and delivering it to the target site once applied to the skin

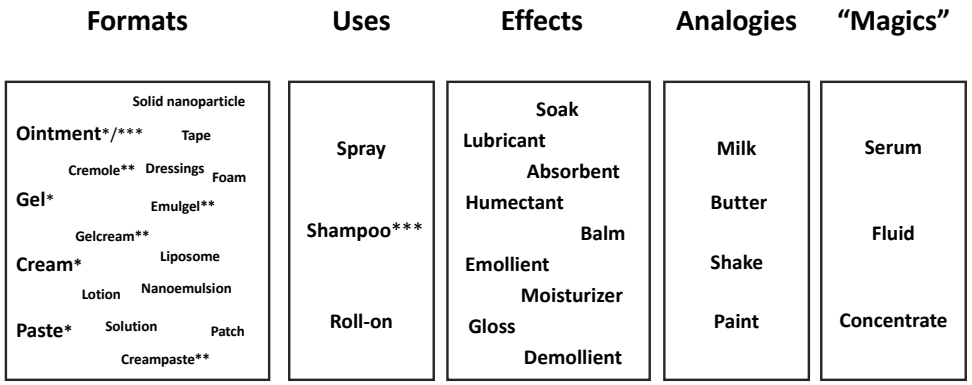

Figure 2 Widely used terms to describe topical vehicles may be grouped according to their formats, uses, effects, analogies or "magic" effects. The various designations describe large product groups (e.g., gel, hydrogel, lipogel, emulgel and gelcream or moisturizer and emollient, etc.) which can be very different in their composition and properties. It is not possible to derive the properties from designations without knowing its exact composition. Colloquial expressions, personal experience and recommendations have shaped our perceptions and expectations of product vehicles. Quality (translucent/sticky), effect (cooling/occlusive) and use/target (young skin/diseased skin) are often associated with distinct product formats (gel/ointment) * Designations of pharmacopeias (1,2); ** Format combinations are often created for marketing purposes; *** Origin and history of vehicle designations have shaped the meaning and perception of vehicles. E.g., the designation 'Ointment' derives from the word 'anointment'. The application of oil (lipophilic) in a religious ceremony. The designation "Shampoo" comes from the Indian language and means "to massage in"

disease involvement and amount of product which can realistically be used and still be physically acceptable to the patient treating him/herself at home has been estimated. A realistic application quantity is rarely more than 5 mg/cm^2. For semi-solid vehicles, the Finger Tip Unit (400-500mg) and for more liquid vehicles a mechanical dosage aid (e.g., pump with weight data per pump stroke) both with dosing tables/instructions have proven value. Frequency of administration and duration of treatment is often determined on an individual basis.

Typical therapy modalities have been developed to avoid adverse effects (corticosteroids, retinoids). Patients apply medicated product on a daily basis only until symptoms improve (corticosteroids) or irritation occurs (retinoids), and then reduce application frequency. On days without medicated treatment, non-medicated products are recommended.

Figure 3a Many topical products contain significant amounts of volatile vehicle ingredients (water, ethanol, propylene glycol, short chained hydrocarbons) evaporating once applied onto the skin (Figure 3b). After application the sum of vehicle ingredients and hence the vehicle format may change dramatically. This phenomenon is coined as the **metamorphosis of the vehicle**. It is often observed and generates a patient and consumer perception that is described as "the product is well absorbed". To illustrate this phenomenon concisely the application of a pressurized product is presented. The primary vehicle is housed in the primary container. It ensures stability of actives during shelf-life. The secondary vehicle delivers the first product encounter with the skin and conveys the application feel. The tertiary vehicle delivers the second encounter with the skin and conveys the skin feel. The latter represents the sum of ingredients after evaporation of all volatile vehicle ingredients. In terms of designations the product format changes from a solution (in the pressurized can) that is sprayed onto the skin to form a foam that collapses to become an ointment

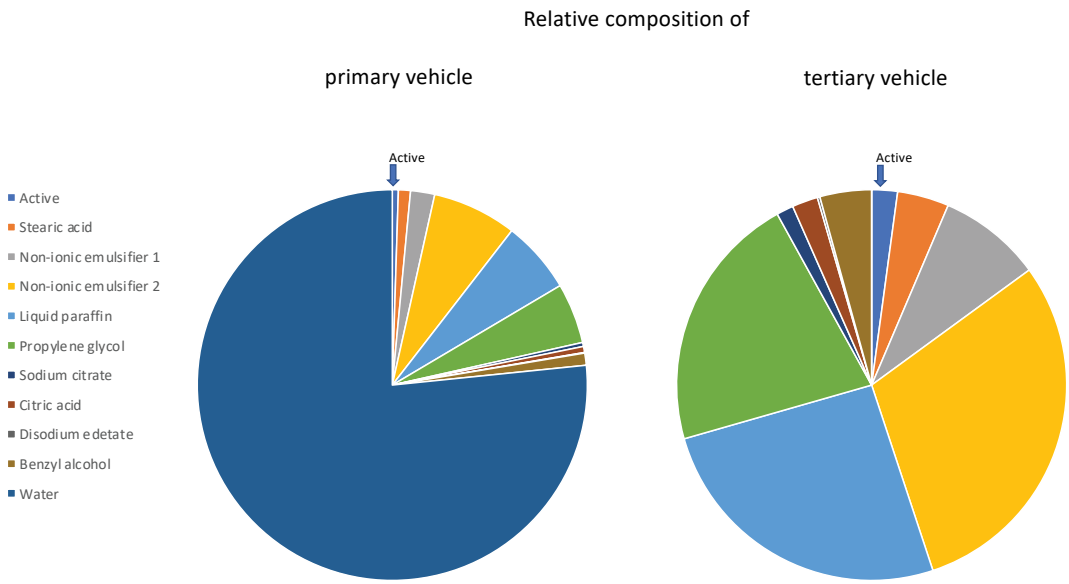

Figure 3b During the metamorphosis the composition of the vehicle ingredients may change dramatically. It is obvious, that the physicochemical sphere for an active in the vehicle alters. As a consequence permeation of an active through skin may decrease (due to precipitation) or increase (due to supersaturation) (3). Effects originating from specific vehicle ingredients are documented (e.g., propylene glycol may be considered as absorption enhancer, petrolatum has an occlusive effect). However, it remains difficult to assign quantitative effect information to a vehicle ingredient if it is part of a complex formulation with many other vehicle ingredients - some of which may evaporate after application

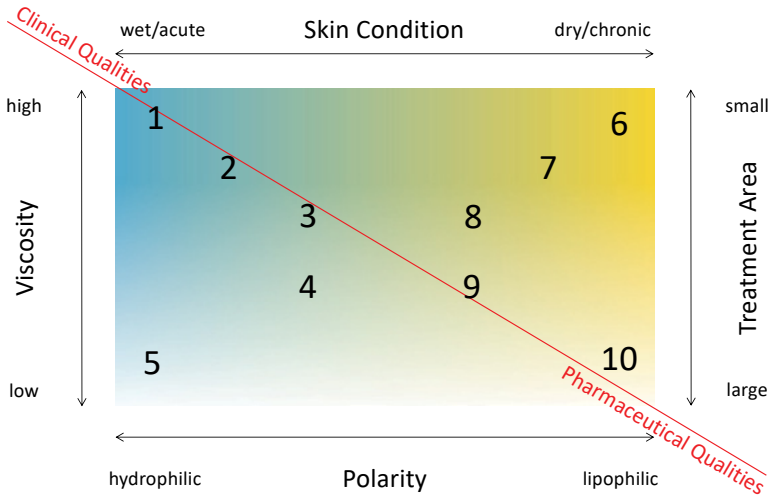

Figure 4 The vehicle choice is based on the nature of the vehicle (polarity and viscosity) and the nature of the dermatosis (treatment area and skin condition). Polarity (x-axis, bottom) and viscosity (y-axis, left) are relevant pharmaceutical vehicle qualities to consider. Hydrophilic vehicles are more suitable for wet/acute and lipophilic vehicles are more suitable for dry/chronic skin conditions (x-axis, top). Low viscosity vehicles are more suitable for larger whereas high viscosity vehicles are more suitable for smaller skin areas (y-axis, right). Typical vehicle formats are: (1) cross-linked hyaluronic acid gel (cubed water); (2) hydro-gel, hydrophilic ointment; (3) o/w-cream; (4) o/w- or hydro-lotion; (5) aqueous solution; (6) lip stick; (7) lipo-gel, lipophilic ointment; (8) w/o-cream; (9) w/o- or lipo-lotion; (10) lipophilic solution (oil). The diagram allows to relate pharmaceutical and clinical qualities. A sensory evaluation of product polarity and viscosity by the health care professional, patient and consumer is usually sufficient to make the right choice. To ensure therapy adherence patient's preference for particular vehicle textures, practicability of therapy modalities and prescription of adequate amounts of product are crucial. To increase cosmetic acceptance, visible skin areas should be treated in such a way that it does not worsen the skin's aspect. Facial skin should not be treated with too lipophilic (greasy) vehicles to prevent shining and the scalp is usually treated with solutions containing glycerin as a humectant. Vehicles on intertriginous skin should not increase friction. Vehicles with a high proportion of rapidly evaporating ingredients may be difficult to spread. The washability of a vehicle can be clinically relevant (skin and wound cleansing). It depends on the physico-chemical properties of the vehicle ingredients (hydro-/lipophilic, emulsifying) and not the vehicle format

Localized and systemic adverse effects may occur. Almost any component of a topical product may sensitize or irritate; notable examples include vehicle ingredients (propylene glycol), preservatives, fragrances or actives (corticosteroids). Patients with chronic wounds (incontinence associated dermatosis, leg ulcer) appear to be particularly susceptible. Extensive, frequent and/or long-term application of topical products with small molecular actives (salicylic acid, crotamiton, imiquimod) may lead to considerable systemic absorption. Due to a different body weight to body surface ratio this hazard is increased in newborns, infants, and children.

Dermatological products are grouped into three different regulatory categories. **Medicinal products** and **medical devices** are used for diseased skin and **cosmetics** are used to protect and to keep the skin in good condition. For medicinal products and medical devices, disease-related claims are allowed whereas for cosmetics it is not allowed. The effect of medicinal products is based on pharmacological and immunological principles and the effect of medical devices is based on non-pharmacological and non-immunological principles. The demarcation between diseased and non-diseased skin is fluent (xerotic vs. dry skin) and, accordingly, all three product categories may be used for gradually similar skin conditions. Terms like **cosmeceutical** – word creation from cosmetics and pharmaceuticals –, **cosmetic active** – analogue to the regulatory term *active pharmaceutical ingredient* – or claims such as **for atopic-prone skin** are used in an attempt to valorize specific products of the category cosmetics. This is sometimes source of confusion, debate and regulatory intervention.

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2 TOPICAL CORTICOSTEROIDS

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In exogenous allergic skin diseases the essential step towards successful treatment is identification and elimination of the culprit allergen within the well-established hierarchy of preventive measures. However, symptomatic treatment options are being used to accelerate clearance of skin lesions: Topical corticosteroids represent the first-line therapy* of all acute, sub-acute and chronic eczematous skin diseases of allergic as well as non-allergic etiology (Figure 1): e.g. allergic contact dermatitis (induced by haptens), protein contact dermatitis (induced by proteins), irritant contact dermatitis (induced by irritants (e.g. wet work) as well as atopic dermatitis (of multifactorial etiology. (*In case of contact allergy to corticosteroids or non-effectiveness or use at special locations (e.g. face, intertriginous skin areas, genital area, capillitium in infants) topical calcineurin inhibitors may be preferable (see Chapter H3).

The benefit of topical applications of corticosteroids in eczematous skin lesions has been well documented since the 1950ies, whereas in contrast the effect of local hydrocortisone on immediate urticarial skin responses has been shown to be minimal.

KEY MESSAGES

- Identification and elimination of the culprit allergen and/or irritant is the essential step towards successful treatment of exogenously triggered skin diseases
- Symptomatic treatment accelerates clearance of skin lesions with topical corticosteroids representing the first-line therapy of all acute, sub-acute and chronic eczematous skin diseases of allergic as well as non-allergic etiology
- The severity and location of skin lesions defines the preferentially applied class of topical corticosteroids
- Based on their ratio of desired *versus* adverse effects, modern topical corticosteroids are preferable
- Beneficial effects on prolonging recurrence-free intervals have been demonstrated for proactive use of corticosteroids (e.g., continued application twice a week after clearance in areas of frequent relapses)

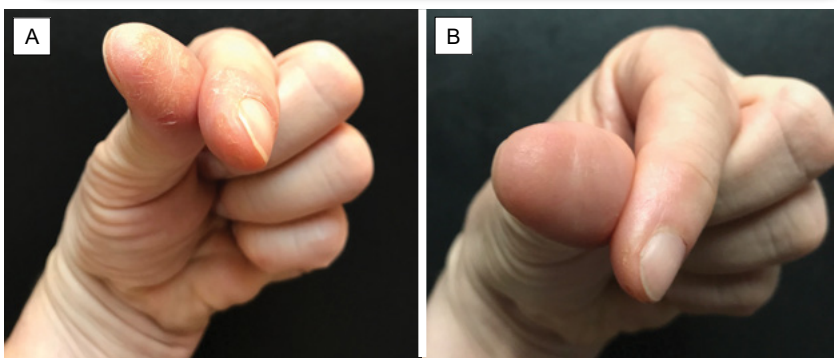

Figure 1 A Chronic fingertip eczema of irritant etiology. B After 5-day-treatment with a class III topical corticosteroid (Halometasone). Treatment of irritant contact eczema contributes to prevention of contact allergy, since preexisting irritation of the skin barrier promotes induction of allergic contact dermatitis

In Europe, four classes of corticosteroids are distinguished (Table 1).

Glucocorticosteroids display anti-inflammatory, immunosuppressive and antiproliferative effects when applied topically to the skin based on intracellular effects in a number of constitutional as well as skin infiltrating cells (Table 2): A key effect of topical corticosteroids is the inhibition of the activation of the Transcription factor NF-kB and resulting thereof inhibition of formation of (pro)inflammatory cytokines.

There are no generally accepted fixed schedules of application, however, several rules apply (Table 2). Treatment with topical corticosteroids shall be guided by the severity, acuity and tendency for relapses of allergic skin disease. Topical glucocorticosteroids are usually used for a limited period or used as interval therapy ("as short as possible, as long as necessary"). Also proactive treatment is an option (Table 2): In areas of observed frequent relapses, after clearance of the eczematous skin lesions, application of the topical corticosteroid is continued twice a week for prophylaxis of recurrences. The indication for strong and very strong tropical corticosteroids (class III, exceptionally class IV) lies in the short-term treatment of pronounced acute or exacerbated eczema or chronic lichenified eczema manifestations (e.g. of the hands).

It is noteworthy to point out, that topical corticoid phobia is commonly reported by patients across cultures and may be associated with nonadherence. It appears feasible for the physician to ask the patient about these unspoken concerns and fears when prescribing topical corticosteroids

TABLE 1

European classes of corticosteroids *	
Active ingredient	**Concentration (%)**
Class I	
Hydrocortisone	0.33; 0.5; 1.0; 2.0; 2.5
Hydrocortisone acetate	0.05; 0.25; 1.0
Dexamethasone	0.03; 0.035; 0.05
Fluocortine butyl ester	0.75
Prednisolone	0.25; 0.4
Triamcinolone acetonide	0.0018; 0.0066
Class II	
Alclometasone dipropionate	0.05
Betamethasone benzoate	0.025
Betamethasone valerate	0.05
Clobetasone butyrate	0.05
Desonide	0.05; 0.1
Desoximetasone	0.05
Dexamethasone	0.08
Flumethasone pivalate	0.02
Fluocinolone acetonide	0.01
Fluocortolone	0.2
Flupredniden acetate	0.05; 0.1
Fluorandrenolone	0.025
Halcinonide	0.025
Hydrocortisone aceponate	0.1
Hydrocortisone buteprat	0.1
Hydrocortisone butyrate	0.1
Methylprednisolone aceponate	0.1
Prednicarbate	0.25
Triamcinolone acetonide	0.025; 0.1
Class III	
Amcinonide	0.1
Betamethasone dipropionate	0.05
Betamethasone valerate	0.1
Desoximethasone	0.25
Diflorasone diacetate	0.05
Diflucortolone valerate	0.1
Fluocinolone acetonide	0.025
Fluocinonide	0.05
Fluticasone propionate	0.005; 0.05
Halcinonide	0.1
Halomethasone	0.05
Mometasone furoate	0.1
Class IV	
Clobetasol propionate	0.05
Diflucortolone valerate	0.3

** (modified from Niedner 1996)*

TABLE 2

Principles and effects of treatment of allergic skin diseases with topical corticosteroids *	
Pharmacological Effects	Topical corticosteroids combine with their receptors, which are found in the epidermis in higher density than in the corium; they inhibit the proliferation in the skin of the epidermal cells, leading to a normalization of the cornification processes; inhibition of the collagen and mucopolysaccharide synthesis is observed in fibroblast, whereas the number of lymphocytes and granulocytes in the skin decrease. Mast cells release their mediators to a lesser extent and melanocytes form less pigment. Vasoconstriction of the vessels is induced.
Strength of topical corticoid	At initiation of topical corticosteroid treatment always the strongest preparation admissible for the specific dermatosis with consideration of its localization and severity should be used. After response of the eczematous skin lesions to the treatment it may be tapered quickly. It is always more feasible to start with a stronger preparation to effectively stop the skin lesions early on than applying -due to misunderstood restrains- too weak preparations with too little effect for too long provoking unwanted side effects.
Cream/ointment base	Besides the active ingredient in a topical corticosteroid preparation also the base contributes to the therapeutic effect: for acute oozing allergic skin reactions an aqueous base is preferable over a greasy ointment base which in contrast, is better for chronic and lichenoid manifestations of allergic skin disease.
Enhancers	Occlusive treatment or wet envelopes increases effectiveness, addition of keratolytics and keratoplastics such as urea or a penetration mediator such as propylene glycol enhance penetration.
Location of application	Unproblematic areas are in particular the capillitium, palmae and plantae. Areas of rather thin skin thickness with enhanced penetration are delicate and prone to unwanted side effects (e.g. skin atrophy): all intertriginous areas (like neck fold, axillary region, inguinal region, genitals, crook of the elbows, hollows of the knee and others. In addition, the face is a problem zone where application of steroids should be avoided.
Specific patient groups	In children and pronounced barrier malfunction in dermatitis increased resorption of topical corticosteroids has to be taken into account when choosing the respective product and class.
Duration of treatment	The therapy of acute allergic skin diseases in general requires a maximum of two weeks. Therefore, the topical corticosteroid preparation should be prescribed in an adequate, but limited quantity.
Frequency of application	Topical corticosteroids are adsorbed in stratum corneum and thereby form a reservoir. That is why a one-time daily application is usually sufficient.
Ending the treatment	Topical corticosteroid treatment cannot be stopped abruptly, otherwise provoking a rebound effect. Tapering of treatment is necessary: e.g. reduction of corticosteroids of class III to class II and finally even to class I (step down therapy). A further reduction of the steroid application is achieved by the reduction of the application frequency (no longer on a daily basis, but every other day alternating with steroid-free ointments or cream bases, then stretched to use every three to four days (interval therapy).
Proactive treatment	Beneficial effects on prolonging recurrence-free intervals have been demonstrated in randomized studies for intermittent use (Sunday/Tuesday/Thursday) of mometasone furoate cream in hand dermatitis as well as proactive use (2–4 times per week, depending on the study) of topical agents containing fluticasone propionate, and methylprednisolone aceponate in the prophylaxis of atopic dermatitis recurrences.

Common unwanted Adverse reactions	Depending on the product and duration of application: Atrophy (unlikely if used correctly), rubeosis, telangiectasias, purpura and striae rubrae distensae, skin infection. If used in the face: perioral rosacea-like dermatitis, which occurs regularly with improper application of steroids in the facial area. Based on their ratio of desired and adverse effects, modern topical corticosteroids with a high therapeutic index (TIX = 2) are preferable. Suppression of the pituitary-adrenal cortex axis does not occur even with extensive topical corticosteroid treatment. Control of cortisol levels during and after intensive treatment with topical glucocorticosteroids is not recommended. It may be considered if >50g clobetasol propionate (class IV)/week is applied. A not uncommon side effect is the development of contact allergy to corticosteroids themselves. It may be considered if skin lesions do not improve under topical corticosteroid treatment or even worsen.
Contraindications	Virus-related skin diseases (e.g. varicella, herpes simplex and herpes zoster), epizoonoses (e.g. scabies or lice) as well as syphilitic and tuberculous skin lesions are excluded from topical corticosteroid treatment as well as akne and perioral rosacea-like dermatitis.

** (modified from Niedner 1996; 2003; Luger et al. 2003)*

and share proactively existing evidence on side effects (not) to be expected when used correctly.

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3 CALCINEURIN INHIBITORS

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KEY MESSAGES

- The topical calcineurin inhibitors (TCIs) tacrolimus (Protopic 0.03% and 0.1%) and pimecrolimus (Elidel 1.0%) are treaments that alter the immune system and are developed for controlling atopic eczema as an alternative to corticosteroids
- Tacrolimus is indicated for moderate-to-severe AD and pimecrolimus is indicated for mild-to-moderate AD
- TCIs can be used short-term to treat flares and also longer-term to prevent them
- The main side effect of TCIs is a burning and itching sensation at the application site which usually disappears within a week of use
- TCIs are licensed to adults and children over 2 years of age but can also be used in children below 2 years
- TCIs do not induce skin atrophy in contrast to corticosteroids which favour their use in sensitive cutaneous areas

The topical calcineurin inhibitors (TCIs) tacrolimus (Protopic 0.03% and 0.1%) and pimecrolimus (Elidel 1.0%) were approved in 2000 and 2001 as an ointment and a cream for treatment of atopic dermatitis (AD) as an alternative to topical corticosteroids in patients from 2 years of age and above. TCIs have an anti-inflammatory activity due to T-helper activity affecting synthesis and release of proinflammatory cytokines. They suppress the synthesis of pro-inflammatory cytokines by binding to the intracellular protein macrophilin-12 also called FKBP in the cytoplasm of the target cells. Tacrolimus has a threefold greater affinity to FKBP than pimecrolimus.

Tacrolimus is indicated to moderate-to-severe AD for short-term treatment and long-term intermittent treatment of flares as well as for proactive therapy twice weekly for prevention of flares in adults and children. Pimecrolimus is indicated in mild-to-moderate AD. Although pimecrolimus is not licensed for proactive management it may be used in the prevention of acute exacerbation of AD and can be used intermittently with corticosteroids. The anti-inflammatory potency of tacrolimus is similar to an intermediate potency corticosteroid where as pimecrolimus is less potent. The safety profile of long term use of TCIs of 4 and 5 years has not given any reason of concern in children above 2 years of age and adults. Less data is available in children under 2 years of age.

Tacrolimus ointment and to lesser extent pimecrolimus cream may cause burning sensation at the application site during the first days but usually resolves within one week after initiation. If necessary non-steroidal anti-inflammatory agents or paracetamol can be recommended during the first days of treatment. The side effects appear more often if applied to acutely inflamed skin. Acute flares are suggested to be treated with topical corticosteroids initially before switching to TCI.

Generalized viral cutaneous infections as eczema herpeticum and eczema molluscum have been observed during treatment with TCIs, but no increased risk was observed in clinical trials. An increased background incidence of lymphoma has previously been re-

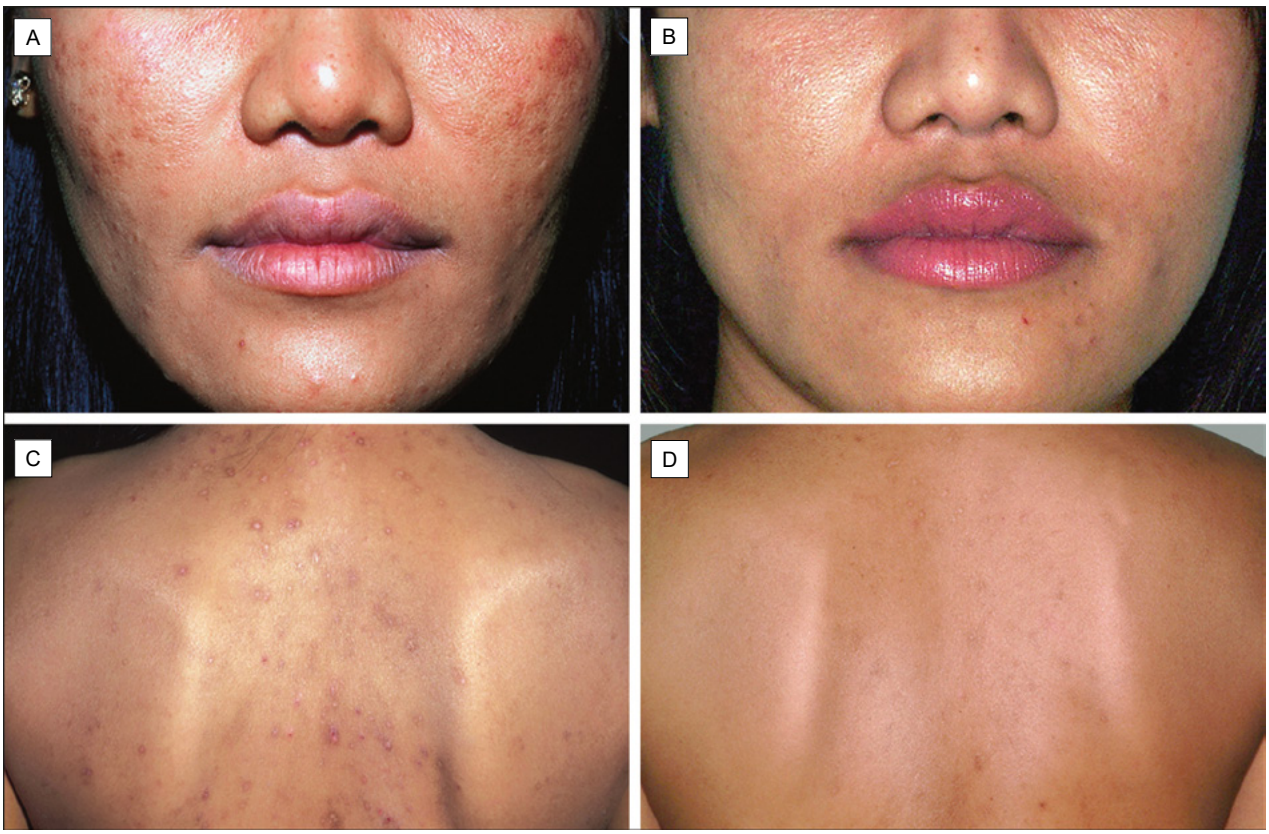

Figure 1 A and C, Before treatment with topical 0.1% tacrolimus; B and D, after treatment. Ref: Arch Dermatol. 2005;141:1203-1208

garded as a safety concern in patients treated with TCIs. However there is no scientific evidence of an increased risk of lymphoma or other malignancies due to topical treatment with TCIs.

TCIs do not induce skin atrophy in contrast to corticosteroids which favour their use in sensitive cutaneous areas (face, intertriginous sites, anogenital area) when need of prolonged management. Effective sun protection is recommended during treatment with TCIs. TCI application does not interfere with vaccination efficacy.

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4 PROACTIVE THERAPY OF ATOPIC DERMATITIS

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Proactive therapy of atopic dermatitis (AD), consisting of long-term intermittent anti-inflammatory therapy after an initial intensive anti-inflammatory treatment phase, has been suggested more than 10 years ago. This concept is based on the finding that flares tend to recur in the same areas in the individual patient and subclinical inflammation has been shown histologically in previously affected areas (Figure 1 and 2).

Proactive therapy is intended to prevent flares of AD, stabilize the skin and thus improve quality of life. It has been hypothesized, that effective disease control may also reduce the rate of sensitizations via skin in early childhood eczema.

KEY MESSAGES

- Proactive therapy aims at long-term stabilization of eczematous skin lesions and thereby improving quality of life of affected patients
- An anti-inflammatory drug is applied topically twice weekly on previously affected areas after an initial stabilization phase of more intensive treatment
- Patients need thorough explanation of the concept
- Long-term studies with modern glucocorticosteroids are needed to prove safety

CLINICAL TRIALS

In randomized controlled trials patients were instructed to use the anti-inflammatory study drug (fluticasone propionate, methylprednisolone aceponate and tacrolimus respectively) on a daily basis until (near) complete disappearance of actual lesions (1-4 weeks) followed by long-term (3-12 months) twice weekly application on initially affected areas. The control group had placebo for intermittent application. In all studies the proactive treatment regime was more efficacious to prevent flares. The amount of the anti-inflammatory drug used was higher in the proactive group. Effects on quality of life were only modest in these studies. A study from Japan found lower serum TARC (thymus and activation-regulated chemokine) levels and less increase in specific IgE against house dust mites in a group of children (3 months to 7 years) treated for 1 year with proactive therapy compared to standard care, pointing towards a preventive effect regarding aeroallergen sensitization. Looking at skin microbiome proactive therapy seems to reduce microbial shift toward *Staphylococcus aureus* during flares of AD.

DAY-TO-DAY ROUTINE

In day-to-day routine, patients / parents need thorough explanation of the proactive treatment concept. Individual anxieties concerning long-term use of anti-inflammatory drugs have to be addressed. A written individual therapeutic plan and a follow-up appointment are helpful. In a real-life setting patients learn to titrate down the application frequency to maintain adequate disease control, ranging from one to three times weekly. Most patients realize marked stabilization of their skin condition along with an important improvement of quality of life after a few weeks. In infants parents may even notice a development leap once the itch-scratch

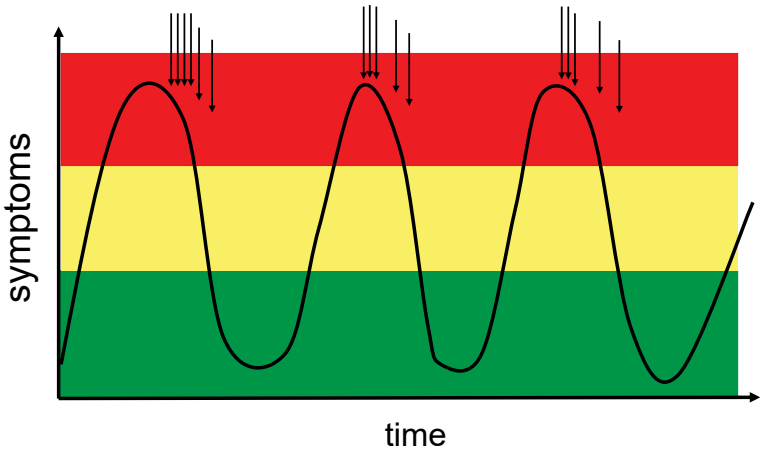

Figure 1 Conventional therapy - application of topical glucocorticosteroids/calcineurin inhibitors

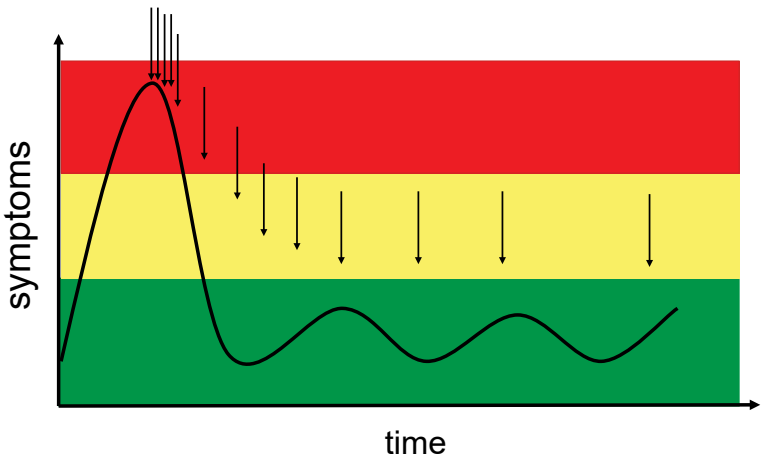

Figure 2 Proactive therapie - application of topical glucocorticosteroids/calcineurin inhibitors

cycle is interrupted and disturbed sleep is restored.

UNMET NEEDS

Only tacrolimus has been licenced for long-term intermittent use. Studies on proactive therapy with modern corticosteroid creams are needed to prove long-term safety.

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5 WET WRAP THERAPY

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Topical treatment is still the mainstay of therapy in various inflammatory skin diseases including atopic dermatitis (AD). Anti-inflammatory pharmacotherapy encompasses the application of topical corticosteroids (TCS) in conjunction with emollients. Commonly, acute flares can be controlled with topical therapy. In severe and recalcitrant cases, efficacy of external treatment can be limited due to inadequate penetration of TCS or scratching as an aggravating factor. In this context wet wrap therapy (WWT) has been established as a way of escalation in order to avoid systemic treatment. Although several treatment schemes exist, they share basic principles (Table 1): After application of the anti-inflammatory medication or emollient on the lesional skin and emollient on non-lesional surrounding skin, the affected part of the body is covered by a moist inner layer followed by a dry outer layer. Depending on the extent and distribution of the skin lesions, usage of garments, bandages or even pyjamas can be considered. In contrast to emollients TCS should be restricted to short-term use and lesional skin due to possible side effects. Successful practical implementation demands special patient training and close follow ups to monitor efficacy and possible complications of WWT. The rationale for WWT is improvement of skin hydration, enhanced absorption of the external drug or emollient and relief of pruritus by cooling of the skin. Moreover, the moist bandages or garments serve as a physical barrier to prevent scratching and foster the recovery of the epidermal barrier (Figure 1). WWT with TCS has been reported to be beneficial in various pruritic dermatoses, most commonly in AD (Table 2). But overall evidence is low due to methodological weakness, variations and small sample sizes of the currently available studies. Experience from clinical practice suggests that TCS are more efficient than emollients only in combination with wet wrap

KEY MESSAGES

- Wet wrap treatment (WWT) is defined as application of emollients, topical corticosteroids on lesional skin covered by a moist dressing and a dry outer layer
- WWT is well-established in management of atopic dermatitis, but may be also beneficial in other pruritic dermatoses
- Besides improvement of skin hydration, WWT may promote absorption of the external drug or emollient and reduce pruritus

TABLE 1

Procedure of wet wrap treatment
• Cut two pieces of (tubular) bandage or garment for each affected arm, leg or trunk in appropriate length
• Soak one of the two pieces in warm water and squeeze out thoroughly
• Treat lesional skin with cream or ointment (emollient / TCS)
• Apply the moist layer on the topically treated skin
• Put the dry layer on the wet dressing
• Wet wraps should be in place for at least 30 minutes, but can be left on overnight as well

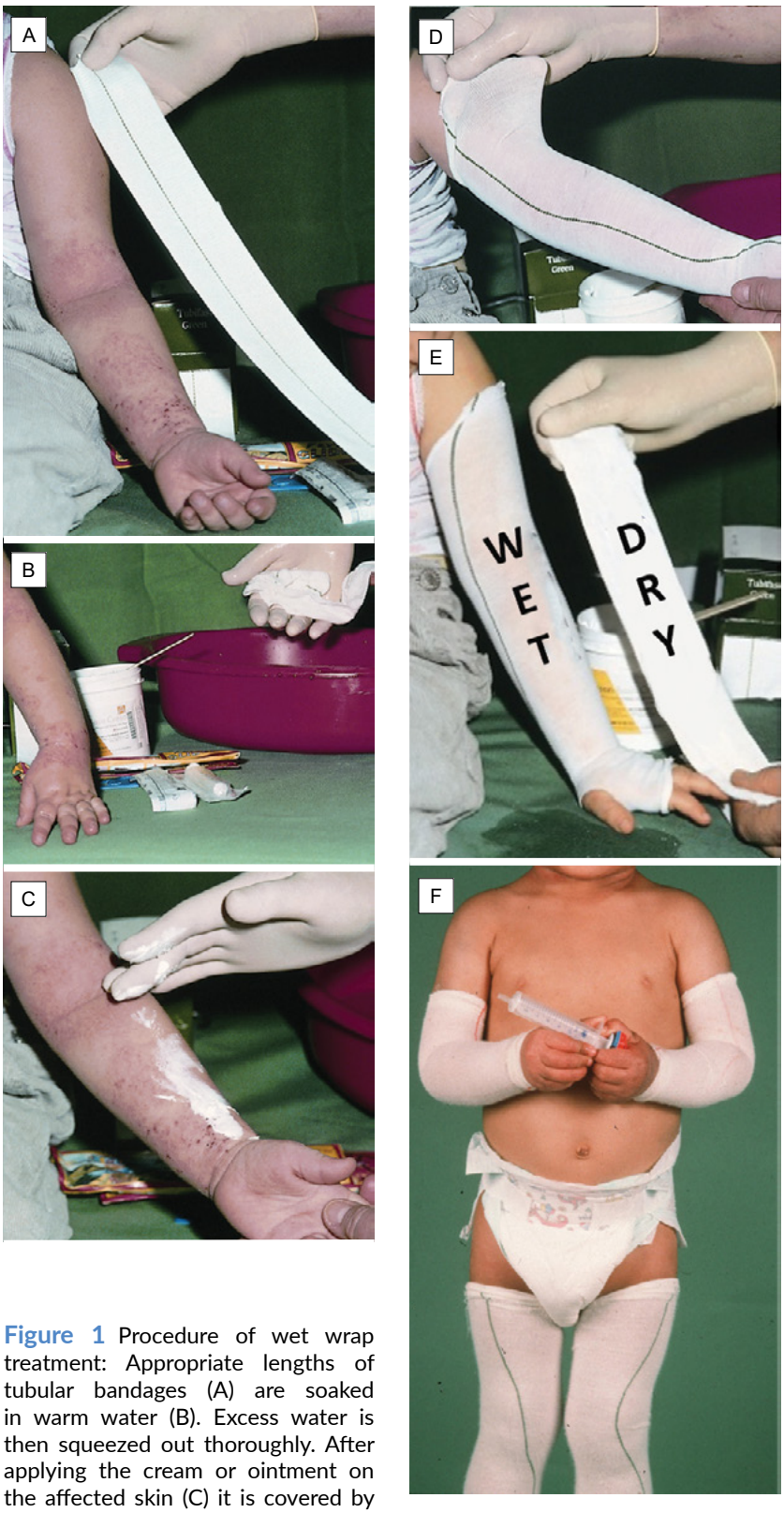

Figure 1 Procedure of wet wrap treatment: Appropriate lengths of tubular bandages (A) are soaked in warm water (B). Excess water is then squeezed out thoroughly. After applying the cream or ointment on the affected skin (C) it is covered by the wet dressing (D). Above this the second dry layer is placed (E, F).

TABLE 2

Wet wrap treatment (WWT) can be considered in a wide range of inflammatory and especially pruritic skin conditions. WWT is well-established in management of atopic dermatitis

- Atopic dermatitis
- Psoriasis
- Cutaneous T-cell lymphoma
- Prurigo nodularis
- Pityriasis rubra pilaris
- Erythema solare
- Nonspecific conditions: erythroderma, pruritus

dressings, but there is conflicting data if diluted TCS might be as effective as concentrated TCS in WWT. Possible local (bacterial or viral superinfections, folliculitis, striae distensae) or systemic (temporary suppression of hypothalamic-pituitary-adrenocortical-axis) side effects of WWT seem to be rare. Larger randomized and controlled studies are necessary to make final conclusions on actual efficacy and safety of WWT in management of AD and other inflammatory skin conditions.

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6 ALLERGEN IMMUNOTHERAPY PRINCIPLES AND MODE OF ACTION

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HISTORY

Prior to the discovery of allergen immunotherapy (AIT), Leonard Noon made the initial observation of effective desensitization in patients with hay fever upon prophylactic injection of grass pollen extract. This led to the first rush immunotherapy protocol and a controlled clinical trial of grass pollen immunotherapy. In continuation, major advances of AIT were apparent from studies confirming disease modifying effects and long-term benefits of AIT to grass pollen, lasting several years upon treatment discontinuation when administered either subcutaneously (SCIT) or sublingually (SLIT).

KEY MESSAGES

- Allergen immunotherapy (AIT), administered either subcutaneously (SCIT) or sublingually (SLIT), is a disease-modifying treatment with long-term clinical benefits upon discontinuation of treatment
- Mechanism underlying SCIT includes the modulation of both innate (ILC2s) and adaptive (Th2, Th2A and Tfh cells) immune responses
- Immune tolerance following AIT is associated with an increase in inducible T regulatory cells (iT_R35, Tr1 and Th3 cells), as well as FoxP3$^+$ T regulatory cells
- IL-10$^+$ B regulatory cells and allergen-specific IgG_4 blocking antibodies are induced following AIT and are also associated with immune tolerance

MECHANISM

The mechanism of AIT involves immune modulation of effector cells, as well as innate and adaptive immunologic responses (Figure 1). A double-blind trial of SCIT to grass pollen illustrated improvement of clinical symptoms which is associated with a reduction in mast cells, basophils and eosinophils in the nasal mucosal. Similarly, both SCIT and SLIT reduced intracellular basophil histamine release, as quantified using fluorescently-labelled diamine oxidase (DAO) at a single cell level.

The effect of AIT has also been illustrated in innate immune responses in which grass pollen SCIT, but not 4-months SLIT treatment, effectively blunted seasonal increases of type 2 innate lymphoid cells (ILC2s) and the proportion of IL-13$^+$ ILC2s. Whilst AIT is known to modulate various cells of the immune response, various studies have demonstrated their effect on T cells. One such example is the GRASS trial illustrating that both modes of AIT are associated with suppression of peripheral tetramer-positive Th2 cell numbers and local nasal Th2 cytokines following nasal allergen challenge. More recently, it was demonstrated that patients who benefited from AIT had reduced levels of allergen specific Th2 (Th2A) cells and T follicular helper (Tfh) cells, both of which are novel subsets of T cells.

Immune tolerance following AIT has been associated with an increase in FoxP3$^+$ regulatory T cells (Tregs), with further molecular studies associating this increase with demethylation of FoxP3 CpG sites in Tregs of the active group. Inducible Tregs that include IL-10$^+$ (Tr1), IL-35$^+$ (iT_R35), TGF-β$^+$ (Th3), as a result of AIT, have also been shown to modulate aller-

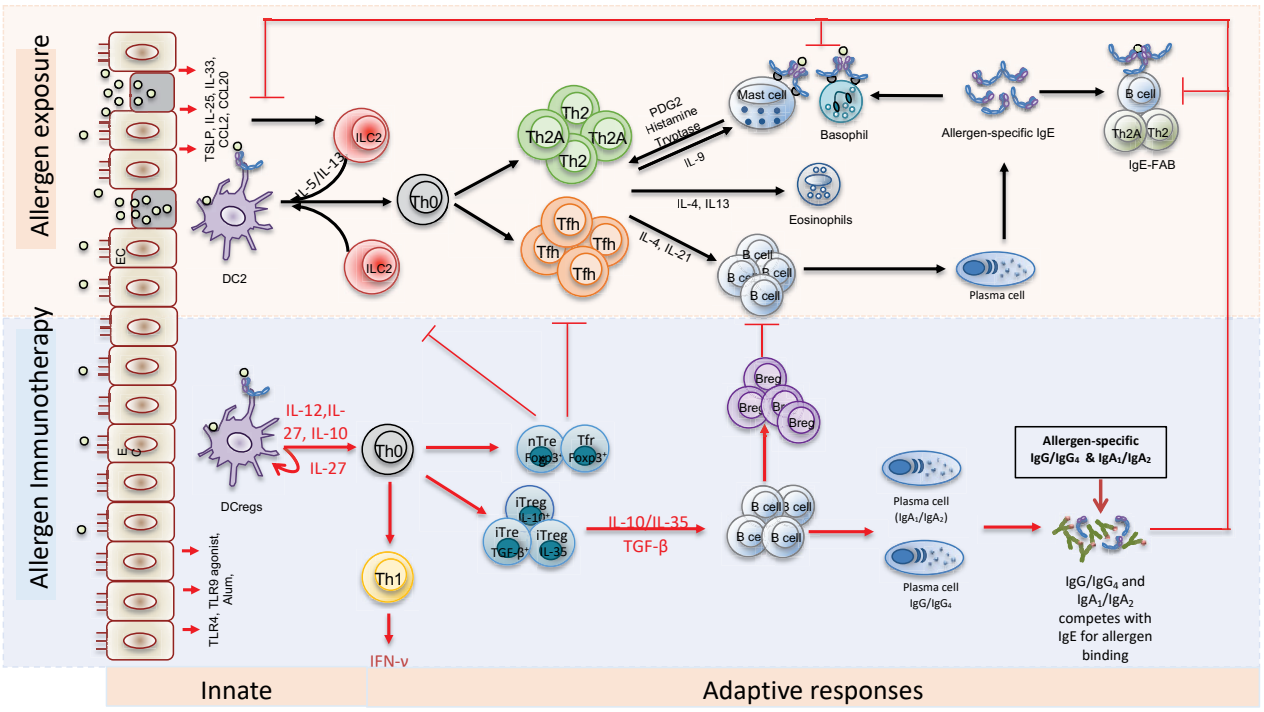

Figure 1 Mechanism of Allergen Immunotherapy (Taken from Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol. 2017;140:1485-98.)

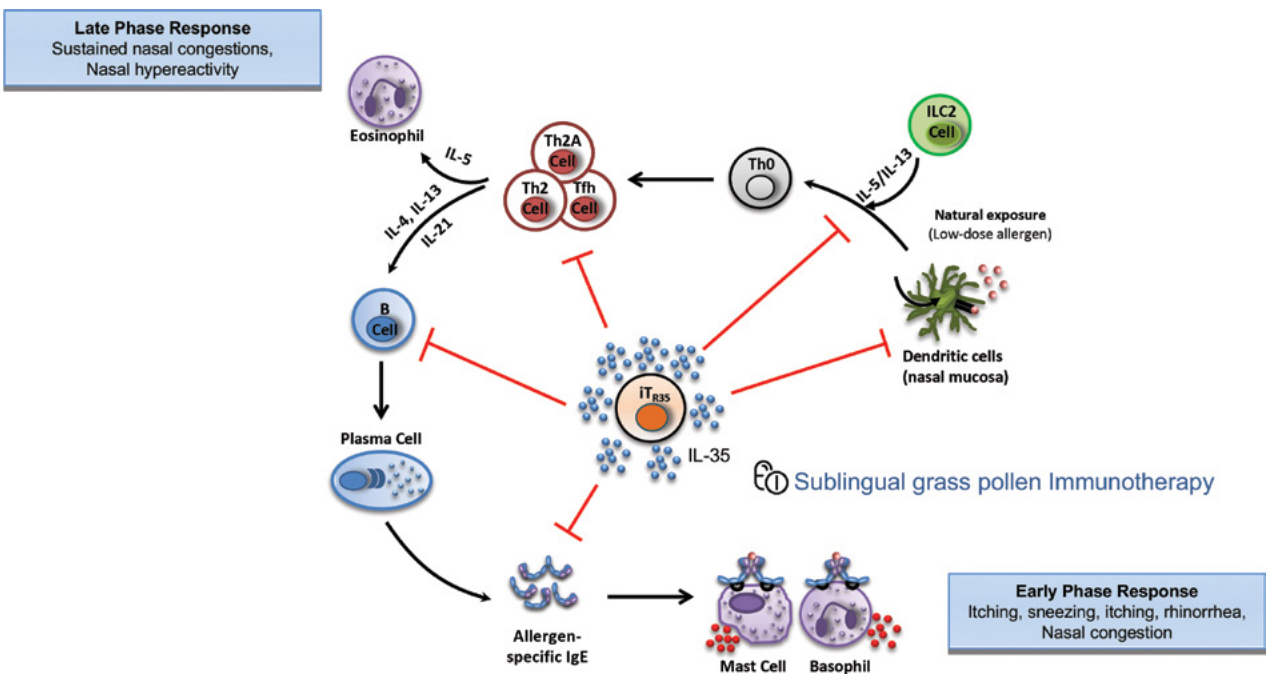

Figure 2 Sublingual allergen immunotherapy is associated with an increase of IL-35 cytokine and inducible IL-35 T regulatory (iT_R35) cells, with regulatory capacity (Taken from Shamji MH, Layhadi JA, Achkova D, Kouser L, Perera-Webb A, Couto-Francisco NC, et al. Role of IL-35 in sublingual allergen immunotherapy. J Allergy Clin Immunol. 2019;143:1131-42 e4)

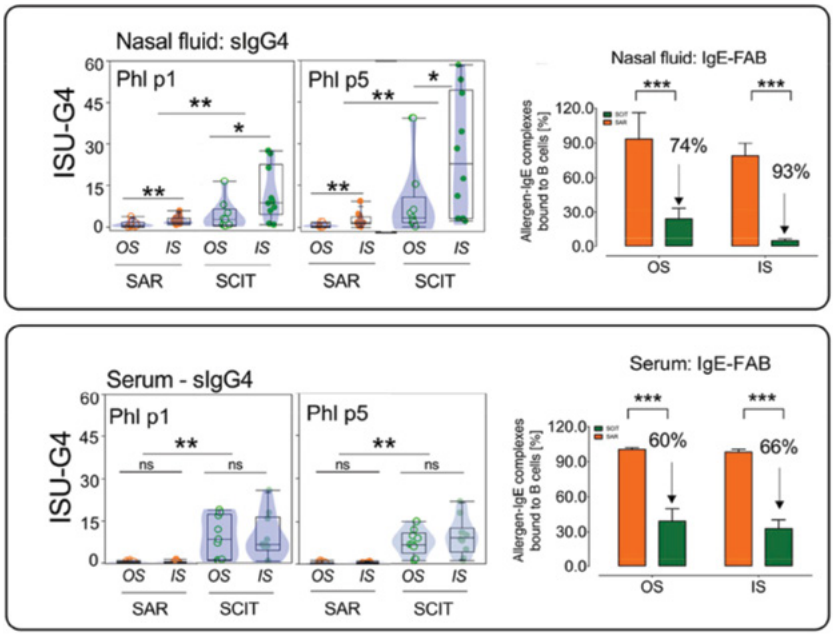

Figure 3 Subcutaneous allergen immunotherapy induces local production of allergen-neutralizing IgG_4 antibodies, which can block IgE-mediated responses. IgE-FAB (IgE-Facilitated Allergen Binding Assay), OS (Out of Season) and IS (During the grass pollen season). (Taken from Shamji MH, Kappen J, Abubakar-Waziri H, Zhang J, Steveling E, Watchman S, et al. Nasal allergen-neutralizing IgG4 antibodies block IgE-mediated responses: Novel biomarker of subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol. 2019;143:1067-76.)

gen-mediated T-cell proliferative responses and Th2 cytokine production (Figure 2). Additionally, IL-10$^+$ B regulatory cells, induced following AIT, are thought to be responsible for the generation of allergen-specific IgG_4 blocking antibodies which can inhibit FcεRI and FcεRII-mediated proallergic responses (Figure 3). In contrast to common pharmacotherapies, AIT is currently regarded as the only disease-modifying treatment for allergic diseases. However, the associated drawbacks highlight the continuing need for a safer and more effective treatment with enhanced patient compliance.

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7 ALLERGEN IMMUNOTHERAPY: SUBCUTANEOUS (SCIT) AND SUBLINGUAL ROUTES (SLIT)

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KEY MESSAGES

- Allergen immunotherapy (AIT) is a unique treatment for allergic rhinitis and allergic asthma
- AIT aims for allergen-specific long lasting immunological and clinical tolerance and can modify the natural course of respiratory diseases
- Depending on climate and geographical conditions, tree, grass and weed pollen or various mites are the most important allergen sources applicable for AIT; furry animal or mold allergy are indications for AIT in selected cases
- AIT is provided by repeated applications of high allergen doses for at least three years
- The two most commonly prescribed AIT routes are subcutaneous (SCIT) and sublingual immunotherapy (SLIT), with comparable efficacy; SLIT has a superior safety profile
- Differences in allergen preparations require product-specific evaluations for proper clinical documentation regarding AIT efficacy and safety

GOALS OF ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy (AIT) represents an important treatment for IgE-mediated allergic respiratory diseases with underlying Type 2 (T2)-inflammation, like allergic rhinitis (AR) and allergic asthma (AA). AIT can achieve long-lasting immunological and clinical tolerance after repeated application of high doses of allergen products from pollen, mites and certain molds for at least three years. Decreased symptoms and medication use and less progression of allergic diseases (i.e. from AR to AA) are ultimate goals of AIT.

DOSING AND APPLICATION ROUTES

Only high doses will lead to allergen-specific immunological tolerance. Two major routes are globally used for AIT:

a) Subcutaneous immunotherapy (SCIT) with monthly injections in the subcutaneous tissue (upper arm approx. i.e. 10 cm above the elbow) (Figure 1a, 2a).

b) Sublingual immunotherapy (SLIT) placing daily droplets or tablets with defined allergen content under the tongue (Figure 1b, 2b).

MOVING PROTEIN ALLERGENS THROUGH THE SKIN OR THE MUCOSA

Both AIT applications aim for effective allergen uptake by antigen-presenting cells (APC) and subsequent transport to (regional) lymph nodes (Figure 3). Future research might show, how much allergen can be processed by skin and mucosal APCs to modify innate and adaptive immune responses. Thus, dose finding studies for safety and efficacy are important clinical development steps for AIT products before pivotal randomized controlled field studies and subsequent market authorization.

COMPLEX IMMUNOLOGICAL MECHANISMS

Allergen-specific tolerance evolves through APC, T and B-cell interactions, activation of tolerogenic regulatory immune cells and production of blocking antibodies, i.e. of subclass IgG_4. Reported immunological changes are consid-

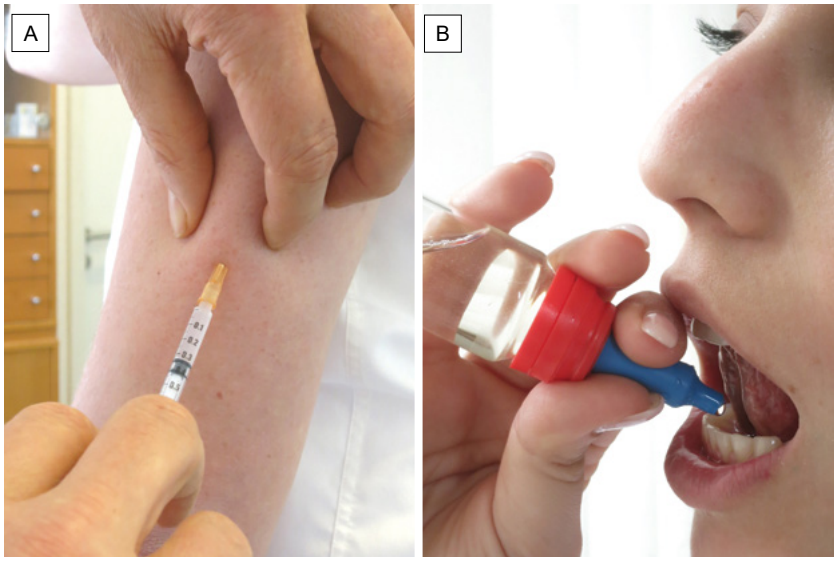

Figure 1 Allergen application for subcutaneous (SCIT) (1a) and sublingual immunotherapy (1b)

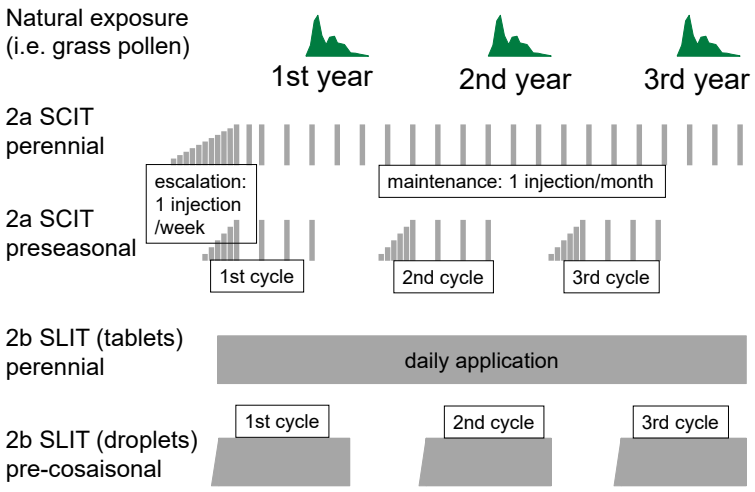

Figure 2 Common AIT application schemes of allergen products using SCIT (2a, upper part) or SLIT (2b, lower part) for seasonal allergies (i.e. grass pollen). Abbreviations: SCIT: subcutaneous immunotherapy (each single line: one subcutaneous injection); SLIT: sublingual immunotherapy (solid bars: daily sublingual application). (modified from Mahler V et al. 2019)

ered potentially necessary, but not sufficient conditions for the clinical success of AIT. Displaying a fascinating model, global AIT research has uncovered complex immune interactions rather than one single mechanism. The search for appropriate biomarkers will continue to better predict the success of SCIT or SLIT in the future.

DIFFERENCES IN GLOBAL ALLERGEN EXPOSURES AND PRODUCTS

Global allergen exposures vary due to climate, geography and cultural variables. In some countries respiratory allergies to proteins from tree, grass or weed pollen are highly prevalent, in others various mites are dominating allergen sources. Allergen products are available as non-modified, aqueous, chemically modified (allergoids), particle (i.e. alum)-adsorbed extracts, adjuvanted, or synthetic allergen constructs. Ready-to-use products or individual allergen mixes differ considerably due to variable qualitative composition and quantitative potency and show heterogeneous clinical results.

CLINICAL UTILITY FOR ALLERGIC DISEASES

Indication, proper application, efficacy and safety of AIT have been summarized in international guide-

lines and positions. Currently, large randomized placebo-controlled field studies provide robust evidence not only for SCIT, but particularly for (timothy) grass, ragweed, birch, red cedar pollen and mite SLIT tablets and few aqueous SLIT products. Thus, AIT has adopted evidence based medicine principles and will maintain a cornerstone in the treatment of allergic respiratory diseases (Figure 4).

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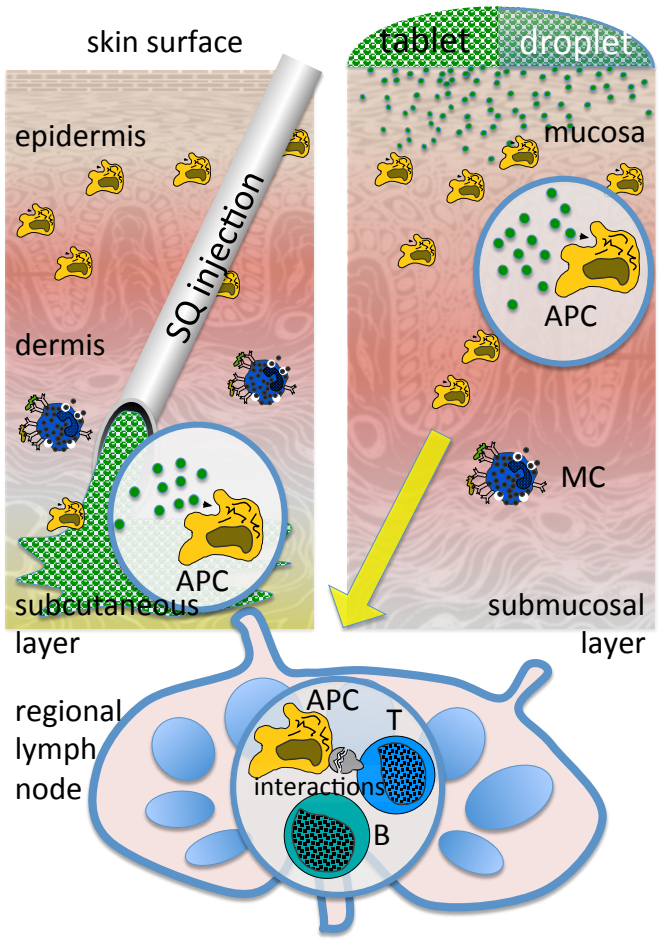

Figure 3 Allergen uptake after subcutaneous SCIT injections (left panel) and mucosal SLIT applications of tablets or aqueous products (right panel) under the tongue. Capacity of regional antigen presenting cells (APC) to process protein allergens might determine successful modification of allergic immune responses in regional lymphoid tissues. Abbreviations: APC: Antigen presenting cell, B: B cell, MC: mast cell, T: T cell

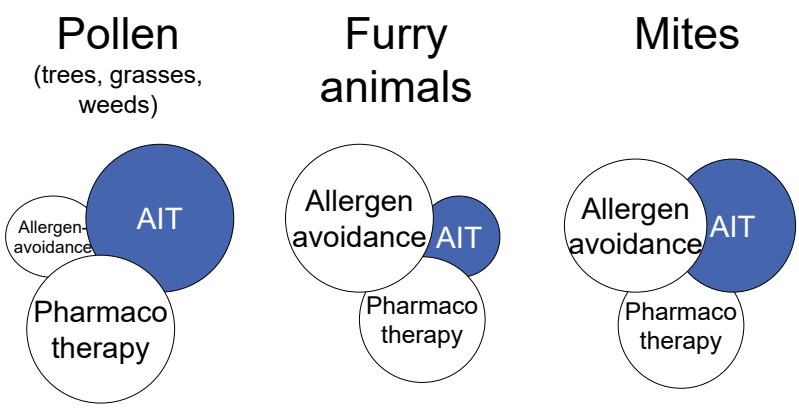

Figure 4 Treatment options for allergic rhinitis and/or asthma depending on the relevant allergen sources

8 EPICUTANEOUS IMMUNOTHERAPY

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KEY MESSAGES

- Epicutaneous immunotherapy (EPIT) is a needle-free and currently investigational treatment option for self-management of allergy
- Clinical testing in patients with grass pollen allergy and with food allergies have shown encouraging efficacy
- Occlusive EPIT has proven safe with few and mainly mild adverse events (AEs), while prior tape stripping was associated with both local and systemic AEs
- EPIT is not ready for clinical practice, but it has obtained breakthrough designation status by the U.S. Food and Drug Administration
- Clinical data are lacking regarding long-term safety and efficacy, effects in adults, as well as dosing and dose frequency

Epicutaneous immunotherapy (EPIT) is the method of allergen immunotherapy (AIT) that involves delivery of therapeutic allergens across the epithelial barrier of the skin. The method is not generally approved, but more than a dozen clinical EPIT trials with allergen-containing patches have been performed since 2009, and the method was recently granted a FDA breakthrough designation status.

EPIT targets the high density of Langerhans cells (LCs) in the epidermis, and the LCs have been shown to carry the allergen to draining lymph nodes for activation B- and T-cell responses (Figure 1). The original studies were performed on pollen-allergic patients receiving 10-12 patches on weekly intervals before and during the pollen season. The skin was pre-treated by tape stripping to enhance skin penetration and to induce inflammatory reactions by activation of skin keratinocytes.

Viaskin® is a registered patch system in development. Viaskin® employs occlusion for improved allergen uptake across intact epidermis, the allergen being dissolved through transepidermal water loss. The patch is applied daily at different sites of the back, the first application with a physician, the rest at home, and a titration is performed by keeping the patch for longer time-periods every week, e.g. 3-24 hours per day (Figure 2).

A potential benefit of EPIT is no or few allergic adverse events (AEs) due to the lack of epidermal blood vessels and mast cells. Less AEs are also expected as no bolus of allergen reaches the dermis, hypodermis, or blood circulation.

Recent development of EPIT has focused on food allergies, e.g. peanut allergy in children. As subcutaneous immunotherapy (SCIT) in peanut allergy is considered too risky and the development of an oral immunotherapy (OIT) is still hampered by frequent AEs, the lack of sustained desensitisation, and the implementation of medical supervision, safe and effective methods for peanut AIT allergy are still required. Phase III clinical trials suggested that daily peanut EPIT with Viaskin® for one year increased tolerance to peanut as compared to pre-treatment levels and placebo. The effect was particularly good in children and the EPIT was associated with increased in anti-peanut IgG4 and

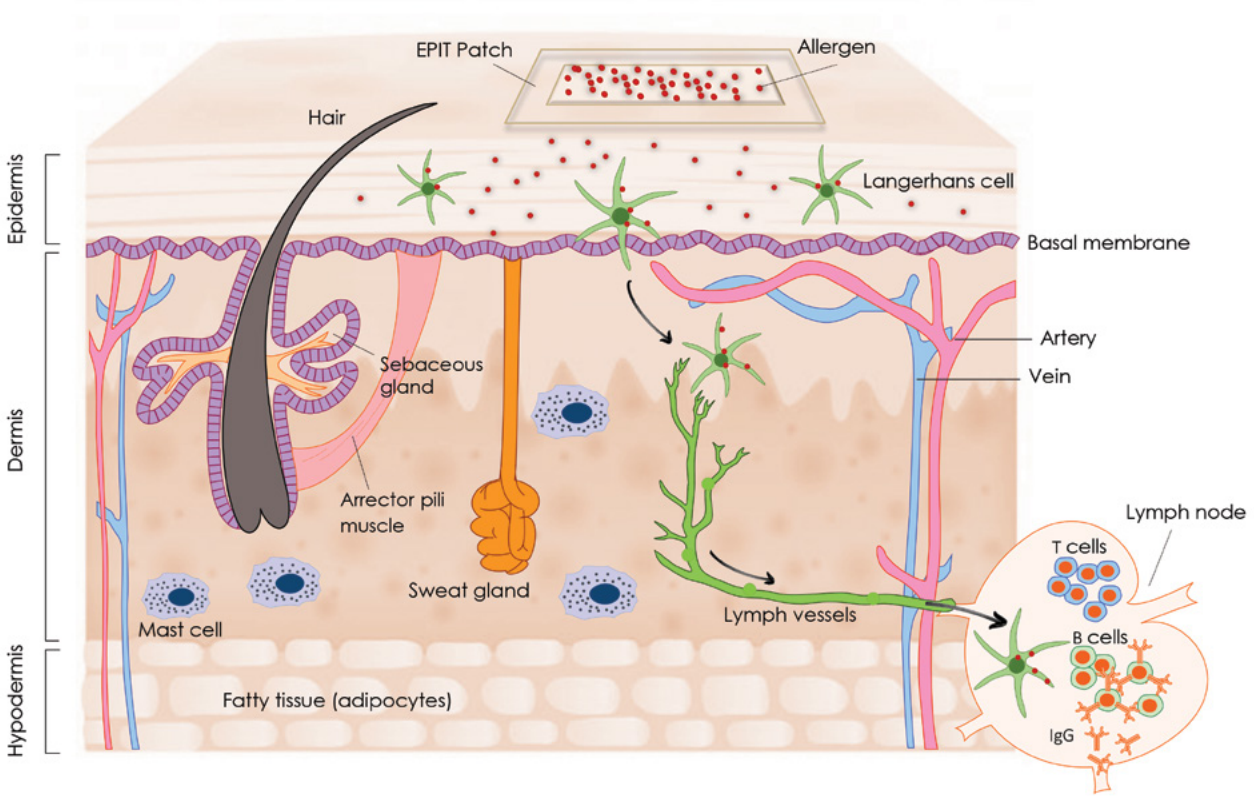

Figure 1 Mechanism of EPIT action. EPIT patch is applied on skin for delivery of allergen to epidermal Langerhans cells (LCs), which are activated (partly by activated keratinocytes) for migration to dermis and subsequently via lymphatic vessels to a subcutaneous draining lymph. Here, the allergen is presented to lymphocytes for stimulation of allergen-specific B- and T-cell responses, including allergen-neutralising IgG antibodies and tolerance-mediating regulatory CD4 T cells. For comparison, AIT by SCIT is administered into the fatty tissue

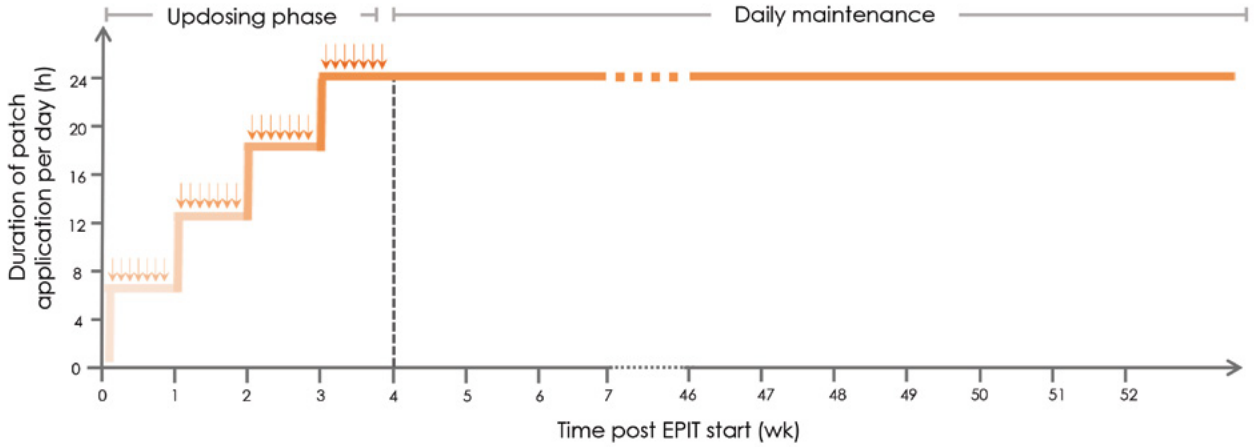

Figure 2 EPIT administration schedule. EPIT with Viaskin® is performed by daily application of the allergen patch for more than one year. During the first weeks, und updosing is performed, by which the patch is kept for longer times on the skin. Typically, the patient keeps the patch for 3 hour per day during the first week then increase the duration of the EPIT application each week, until a maintenance dose of 24h per day is reached

TABLE 1

Potential advantages, disadvantages and open questions related to EPIT

Advantages	Disadvantages & open questions
• Needle-free • Self-AIT at home • Few AEs due to lack of mast cells and blood vessels in epidermis • Few AEs as no allergen bolus administration, but sustained delivery • High frequency of LCs in the skin enables efficient allergen recognition and antigen presentation • Adjuvant free	• Long treatment duration (> 1yr with Viaskin®) • Dosing frequency is unclear (daily with Viaskin®) • Dose-response relationship is unclear • Long-term safety and efficacy is unclear • Skin eczema was reported with pollen EPIT • Unclear if effective also in adults (Peanut Viaskin® was effective in children only) • Protection upon discontinuation of EPIT is unclear • Biomarkers for identification of patients who are likely to benefit from EPIT should be identified • Independent clinical studies are required • Is pre-treatment of skin beneficial, e.g. tape stripping? • Can or should adjuvants be included?

no boost of IgE. Moreover, with no anaphylactic or other systemic allergic reactions and only few and tolerable local AEs, peanut as well as cow milk EPIT have proven very safe.

EPIT poses an encouraging treatment option in allergy, but remains investigational until unsolved questions such as allergen dose, dosing-frequency, effect duration, efficacy in adults, cost-benefit, compliance, and long-term safety become available (Table 1). Moreover, daily application of EPIT may represent a compliance issue.

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9 EDUCATIONAL PROGRAMS FOR SKIN ALLERGY

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KEY MESSAGES

- Structured interdisciplinary educational programs for atopic dermatitis and anaphylaxis have been developed and evaluated
- Distributed learning and learning in groups empower patients solving the problems arising from chronic diseases and increases self-management
- The programs led to significant improvement of knowledge, reduction of anxiety, as well as improvement in quality of life

BACKGROUND

Educational programs aim to empower patients and caregivers in solving the problems arising from chronic diseases. Several educational interventions have been developed in the area of skin allergy, first for bronchial asthma, later for atopic eczema and for anaphylaxis.

Interdisciplinary standardized, structured interventions have been developed in Germany for these diseases, which are proving highly beneficial in the management of patients, children and caregivers of children with these diseases.

EDUCATIONAL PROGRAMS

In Germany, the program of the Neurodermitis Training Association - AGNES for parents of children, children and adolescents with the support of the Federal Ministry of Health has shown to be effective with significant improvement in severity of eczema and subjective severity in all intervention groups compared with control groups as well as in quality of life subscales in an interdisciplinary model project.

In a further study, the Working Group Neurodermitis Training for Adults (ARNE) has demonstrated that adults also benefit from targeted education on how to deal with atopic dermatitis with significantly improvement as compared with the waiting group for coping behavior with respect to itching, quality of life, and eczema severity.

In the wake of the already established and successful training programs for atopic eczema (AGNES and ARNE), the rising numbers of childhood anaphylaxis patients, the lack of empowerment of affected patients in acute emergencies to treat properly (including correct use of the adrenaline auto-injector) and the associated anxiety and uncertainty have been reasons to develop an anaphylaxis training model, to evaluate the model and to establish it throughout Germany. This program led to a significant improvement of knowledge and emergency management competence as well as to a significant reduction of caregiver anxiety. Thus, all of these structured educational programs have demonstrated efficacy in terms of better treatment of the diseases and increase in quality of life or reduction of anxiety (Table 1).

STRUCTURE

AGNES: The educational program for parents, children and adolescents covers 6 sessions of 2 hours. Parents / caregivers of approx. 6 patients are trained by an interdisciplinary team (dermatologists, psychologists, nutritionists).

ARNE: Similar to AGNES, patients are trained by an above-mentioned interdisciplinary team. However, a bigger focus is on psychological aspects.

TABLE 1

Available evaluated standardized structured patient education interventions for skin allergy

Disease	Patients/ Age group	Abbreviation	Duration (Hours)	Number Patients	Team composition	Key aspects
Atopic dermatitis	Adult patients	ARNE	6 x 2 h	6-8	Dermatologist nutritionist, psychologist	Topical treatment, coping strategies, nutritional behavior, prevention
Atopic dermatitis	Parents, children, adolescents	AGNES	6 x 2 h	6-8	Pediatrician or dermatologist, nutritionist, psychologist	Topical treatment, coping strategies, nutritional behavior, prevention
Anaphylaxis	Parents, teacher, children, adolescents, adult patients	AGATE	2 x 3 h	6-8	Pediatrician or dermatologist, nutritionist, psychologist	Use of emergency medication Practical training Allergen avoidance

AGATE: The program covers 2 sessions of 3 hours. The program involves an interdisciplinary team. Focus is the handling of the emergency kit (consists in Germany of three drugs including adrenaline auto-injector), as well as the topic of anxiety, avoidance of the trigger, especially food allergens, although in a group training individual food allergies cannot be discussed.

Learning theoretic considerations prefer the model of distributed learning. The courses are held once a week, so that in the meantime there are opportunities to test the transfer into everyday life (Figure 1).

DISCUSSION

A strategy that maximizes patient and parent education can complement a symptom-oriented therapeutic approach. Such an approach is appropriate for atopic dermatitis, and anaphylaxis, when psychological and nutritional factors and a combination of topical and/or systemic therapies may need to be considered to tackle the underlying multifactorial pathophysiology of these diseases. In addition to treat the symptoms only, giving patients educational support is an important factor in achieving a positive long term outcome and/or safety.

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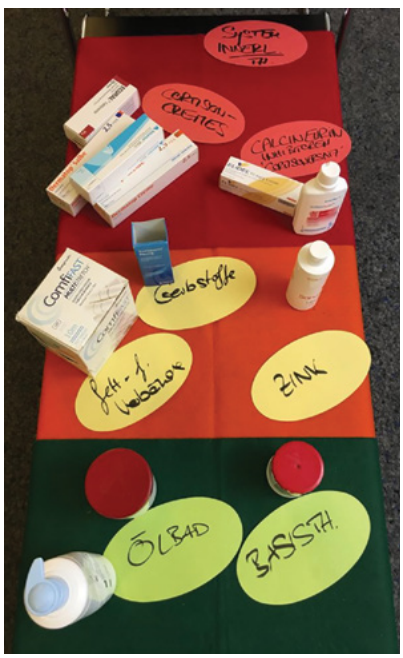

Figure 1 ARNE educational program: Discussion and practical demonstration and use of topical treatment options and their correct use at varying grades of eczema disease severity

Section I

RESOURCES

* Becoming Wireless: Skin allergy in the internet
* Becoming Wireless: Mobile Health Technologies in Skin Allergy Care
* Economic burden of allergic diseases

1a BECOMING WIRELESS: SKIN ALLERGY IN THE INTERNET

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KEY MESSAGES

- The internet is an important educational resource for patients affected by skin allergies making knowledge easily available
- E-learning supports continuous training of medical professionals
- The internet facilitates an unbiased population selection in research and makes data publicly shared by patients' available for studies

The internet is involved in the care of skin allergy patients for three main reasons:

First of all, the internet has become an important educational resource for affected patients or families with members suffering from skin allergies. Via different social media channels or via institutional webpages, medical professionals but also patients share their knowledge and experience. Patients also have the opportunity to seek help via specific platforms providing easy access to expert knowledge. In Germany, the opportunity to ask free questions via the webpage of the Department of Dermatology and Allergy at the Technical University in Munich was evaluated revealing that questions were asked not only by patients but also by physicians. In almost 30% of cases, the requests could be completely answered. Nevertheless, the patients' benefit still remains to be proven, as a study including parents of children with atopic dermatitis did not confer any beneficial influence on self-management and disease burden as well as health care costs by web-consultations. Another important aspect is that potentially available false information influences e.g. treatment adherence of patients. Due to warning for side-effects, the internet was found to reduce patients' compliance for topical corticosteroid use to treat chronic inflammatory skin diseases (Figure 1).

Secondly, also medical professionals benefit from internet based knowledge, as e-learning supports medical professionals to keep their knowledge updated. To give an example, innovative e-surveillance systems offer new opportunities for better patients' care by constant collection and analysis of medical data shared between institutions and different professions to gain a broader overview but also to compare regional differences in skin allergies. Moreover, the internet offers excellent training opportunities for medical students providing integrated learning platforms as established for example by the Department of Dermatology at the University of Zurich (Figure 1).

Last but now least, the internet represents a powerful tool for analysis of patients' data in research studies. Information is publicly shared by patients via social media and mobile applications or in questionnaire-based internet studies. Despite ethical implications, internet based studies might facilitate an unbiased population selection involving also data from patients, who are usually not referred to allergy departments with research facilities.

In conclusion, it is of highest importance to provide unbiased information and to carefully evaluate internet-based knowledge to prevent misinformation via online channels for supporting the enormous potential of web-based re-

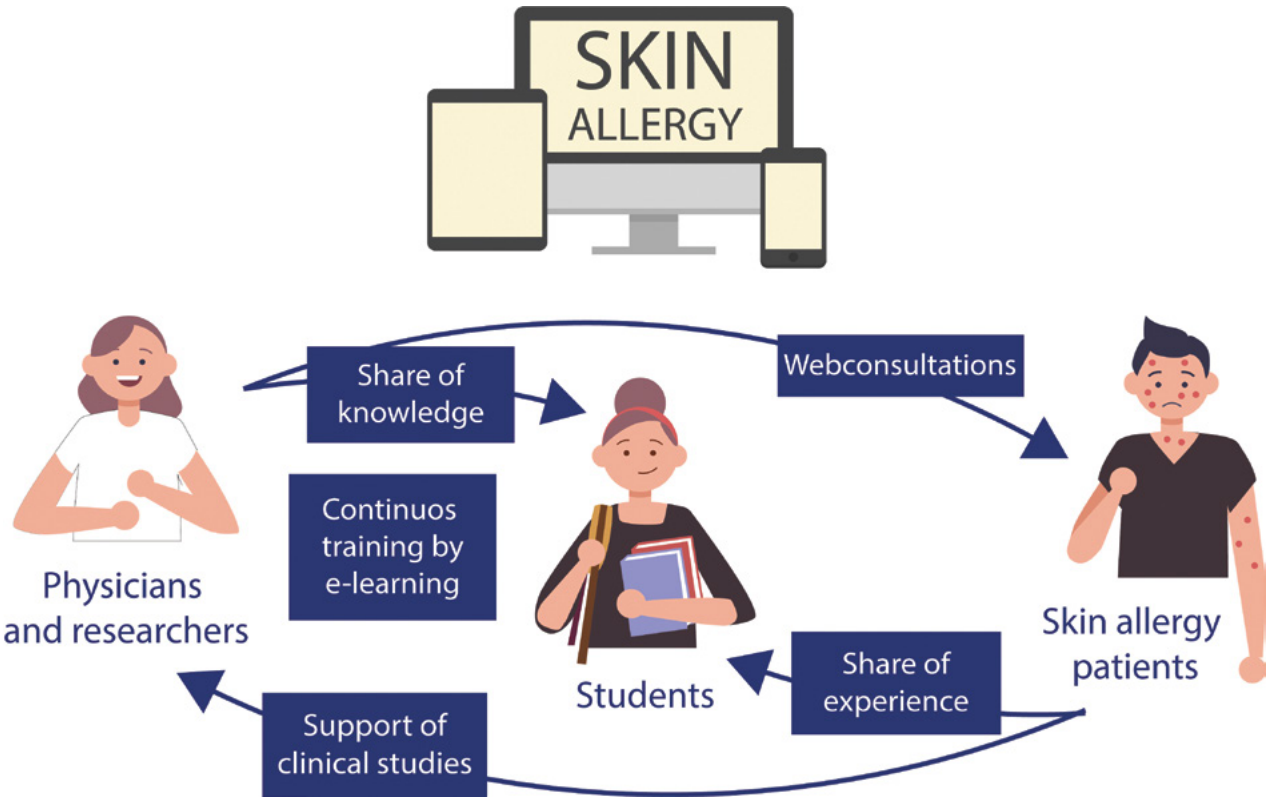

Figure 1 The internet offers ample opportunities for patients affected by skin allergies or for medical professionals working in the field to directly interact, to share information, to support research and to contribute to training activities

sources to be increasingly implemented for research and for care of patients with skin allergies.

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1b BECOMING WIRELESS: MOBILE HEALTH TECHNOLOGIES IN SKIN ALLERGY CARE

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KEY MESSAGES

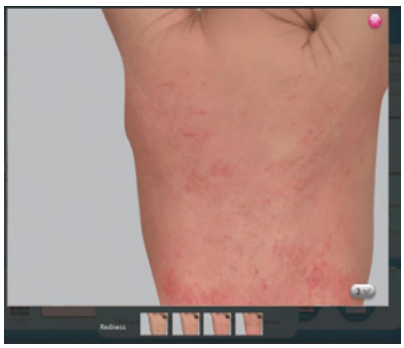
- The variety of digital tools to support patient care in skin allergy is expanding
- Patients and doctors can benefit from mHealth developments
- Quality control and regulatory standards for mHealth technologies are needed

Our daily life is becoming wireless. This is not only reflected by the worldwide number of mobile phone subscriptions which has outgrown the world population, but also by the avalanche of mobile applications (Apps) available to assist us in every aspect of our daily life. Also the area of health and well-being is experiencing a disruptive trend towards digitalization. As new Apps and technologies appear on the market daily, the need for quality control and regulation is growing. This has been underlined by the world Health Organization (WHO), the European Union, national governments and medical associations. The European Academy of Allergy and Clinical Immunology (EAACI) acknowledged the potential of mobile technologies and has set up a Task Force on "Mobile Health (mHealth) & Allergy" in 2016. After evaluating 136 allergy-related Apps, the members of the Task Force created a position paper summarizing general aspects such as legal regulations and evaluation criteria before reporting on the role of mHealth technologies in allergic diseases.

For dermatological allergic diseases such as atopic dermatitis, contact dermatitis, chronic urticaria and cutaneous manifestations of drug hypersensitivity, several approaches have been made by tech developers in order to improve patient care with digital solutions (Figure 1). Once the diagnosis of an allergic skin disease has been made, Apps can support patients and health care professionals (HCP) through symptom monitoring, self-management support, the facilitation of communication between patients and HCPs, telemedicine tools, peer support and data collection for research.

Monitoring of disease severity and its effect on quality of life over time in form of a patient diary may support a better self-control of the disease and provides valuable longitudinal data for the attending doctor. Digital versions of validated questionnaires in Apps and the graphical display of their result scores over time provide insight to patients, caregivers and HCPs into the course of the disease and the effect medication or topical therapy. Some examples of validated instruments to assess the severity of dermatological diseases are ScoradCard, the Patient Oriented Score of Atopic Dermatitis (PO-Scorad) as well as the Atopic Dermatitis Activity Score and the Patient Oriented Eczema Measure of the University of Nottingham. Other specific tools measure the impact of chronic skin diseases on sleep quality, using wearable sleep and/or itch tracker. Medication reminders or adherence apps remind patients to use their medication in time and might help to support action plans.

Informative applications around specific diseases can support self-management of the patients. These tools may also include playful information for children, treatment support, recommendations on a better living with the disease, videos and patient stories. Secure digital data transfer enables pa-

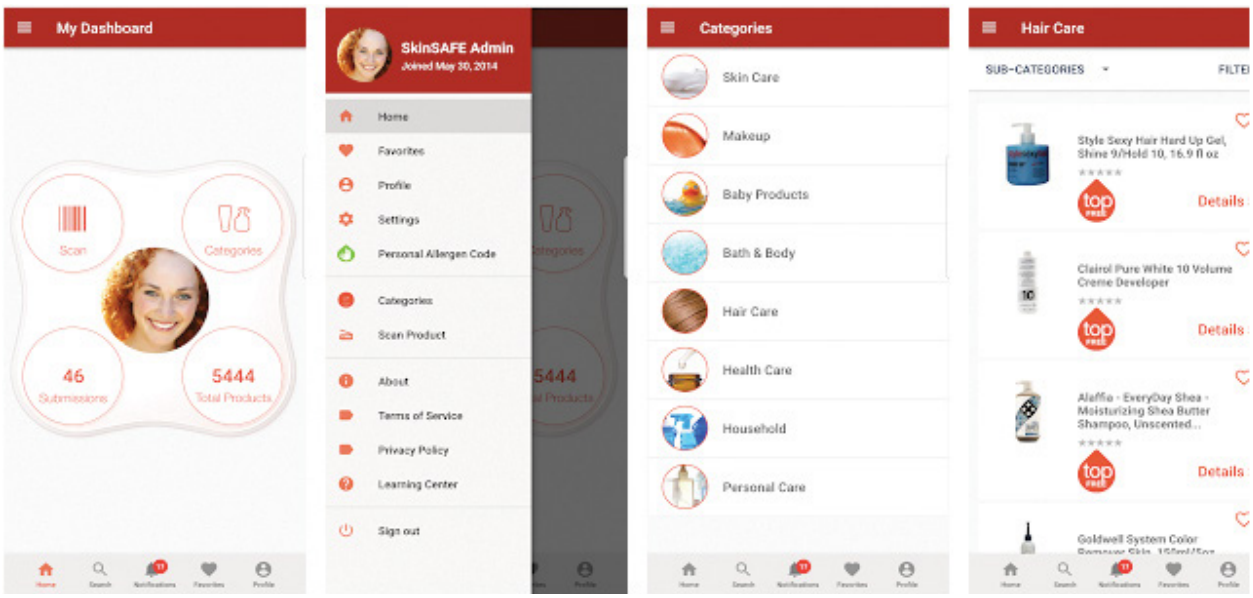


PO-SCORAD

Self-assessment of eczema severity score to better monitor and treat patients with atopic eczema.

- Record of disease severity, including itch
- Graphical display of results over time
- Photo documentation within the App
- Data transmission to doctors

Languages: 23 / Website: https://www.poscorad.com/#/



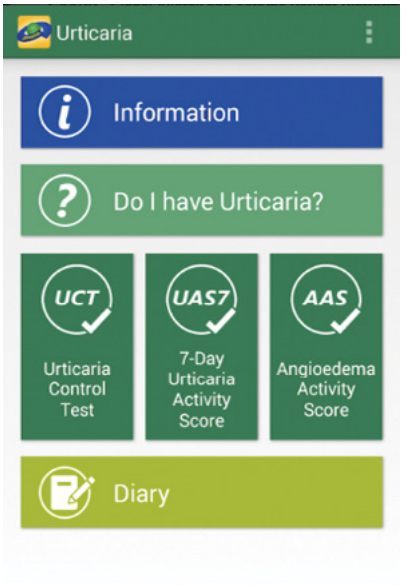
Skin Safe

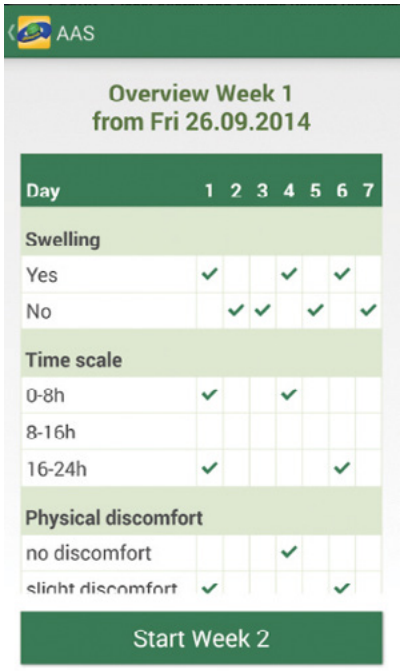
Information about allergens in skin care products for patients with allergic contact dermatitis.

- Creates an individualized allergen list according to patch test results.
- Shows cosmetic products safe for the allergic patient
- After scanning a product: report on contained allergens relevant for the patient
- Personalized list of favorite products

Languages: 1 (English) / Website: https://www.skinsafeproducts.com/apps

Figure 1 Selected examples of mHealth tools for skin allergy care





Urticaria app
Information on and monitoring of urticaria.

- Information on symptoms and diagnosis of urticaria
- Follow-up of the urticaria control test, 7-day urticaria activity score
- and the angioedema activity score over time
- Be aware: developed by the Global Allergy and Asthma patient platform,
- which is sponsored by pharmaceutical companies.

Languages: 2 (English, German). Website: https://play.google.com/store/apps/details?id=at.alysis.urticaria&hl=de

Figure 1 continued from previous page

tients to share photos with their HCP and if agreed by the patient to forward this information between doctors for teledermatological consultations. Further, automated image recognition and digital photo-documentation of skin prick test, patch test and intradermal test results may assist doctors in their clinical routine.

Overall, the role of doctors, and in particular allergists, will be progressively altered with the increase of digital opportunities to improve patient care. EAACI recognizes the advent of the m-Health Era in allergology and contributes to its development proactively.

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2 ECONOMIC BURDEN OF ALLERGIC DISEASES

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KEY MESSAGES

- Allergic diseases have a substantial economic impact including direct, indirect and intangible costs
- One third of suspected occupational diseases are skin diseases
- Out-of-pocket costs, not reimbursed by insurance companies, are substantial for patients with allergic diseases

Allergic skin diseases are associated with a substantial economic burden resulting from direct healthcare costs (utilization of health and disability-related resource), indirect costs related to reduced productivity by for example absenteeism at work as well as intangible costs related to impairment of health-related quality of life.

DIRECT AND INDIRECT COSTS

For atopic eczema yearly costs of 2200 Euro are estimated for direct, 1200 Euro for indirect costs per patient and year. In total, this would mean 1.7 billion Euro per year for 500000 patients in Germany. Annual patient costs for patients with atopic dermatitis for health related quality of life and productivity were analysed using the National Health and Wellness Survey in USA to amount to additional 10 000,-$ every year per patient.

For chronic hand eczema in Germany 3300 Euro are calculated per patient per year implying an annual total of about 1.8 billion Euro for all affected patients. In industrialized countries the yearly incidence of new cases is 1/1000. Notifications for suspected occupational disease comprise 1/3 skin diseases, from which ca 80 % suffer from allergic contact dermatitis, which often forces the patients to give up their profession. Educational programs for a successful change of occupation account to about 100 000 Euro. In Europe costs for occupational skin diseases – and contact allergy is the most common – exceed 5 000 billion Euro per year. Among the notifications for occupational diseases in many European countries contact allergy accounts for 33 %.

For the United States, yearly costs for atopic dermatitis have been estimated to rage around 5.300 billion Dollar ($). The full economic cost for allergic rhinitis is estimated at 24.8 billion $. The annual financial impact of food allergies is reported at 724 $ for direct medical costs, 931 $ out-of-pocket costs and another 285 $ for special diets and allergen friendly food per child per year, respectively. Worldwide, the mean direct medical costs (2081 $) for food allergies per patient per year are much higher than in the United States and even higher than the mean household-level costs (806 $). Mean individual out-of-pocket (1874 $), and opportunity(1038 $) costs were lower than the mean household-level out-of-pocket (3339 $) and opportunity (4881 $) costs. The largest economic burden attributable to food allergies however, are the lost opportunity costs.

In Hong Kong, Malaysia, the Philippines, Singapore, Thailand and Vietnam patients are reported to suffer from perennial allergies and chronic spontaneous urticaria up to 298 days per year when affected resulting in an estimation of the indirect costs of around 100 billion US Dollars every year, equating to about 1000-2000 USD per patient per year.

TABLE 1

Burden of disease in skin allergy

Individual suffering	Component of health costs due to allergic diseases		
	Direct costs	Indirect costs	Intangible costs
Stigmatization	Costs for healthcare professionals (physicians, nurses, technicians, therapists, nutritionists, psychologist etc.) incl. hospital costs	Expenses related to the patient's as well as the patient's family temporary and/or permanent disability due to allergic diseases incl. work absenteeism	Suffering due to the disease (pain, itch) for the patient incl. stress and anxiety concerning behavioural, communication disabilities, mobility disabilities and confidence
Social isolation	Prescription drugs and over-the-counter drugs	Expenses related to the patient's and and patient's family changing jobs	Patient's family suffering incl. stress and anxiety
Sports, leisure restricted	Diagnostic services (incl. laboratory, imaging etc)	Expenses related to patient's family housing (e.g. housedust etc)	
Impact on relationships and sexuality	Purchasing medical equipment	Expenses related to special diets	
Depression	Out-of-pocket costs (not reimbursed by insurance)	Expenses of information and communication technologies (telephone, internet, spent time) due to allergic diseases	
Impaired self-development			
Restricted career opportunities			
Impaired life achievements			

INTANGIBLE COSTS

Due to the special situation of skin allergy patients (also see Ring, this volume) a multitude of expenses have to be taken into consideration for daily life (Table 1). An amount of private expenses has to be paid out-of-pocket by patients without reimbursement by health insurance; this has recently been investigated to be around 900 EURO per year for patients with atopic eczema in Europe.

CONCLUSIONS

Due to the high socioeconomic costs and the often chronic course with bad prognosis management recommendations have to focus on prevention, be it primary to prevent allergic sensitization, e.g. already in infants by topical emollient therapy, or by adequate allergy diagnosis at early stage to find the causative factors and ways to eliminate the contact as good as possible. Occupational counselling is crucial for young individuals with sensitive skin and/or atopic diathesis.

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Figure 1 Economic burden of allergic diseases around the world. Economic burden of allergic diseases in different countries around the world is only available from few countries. Additional research is needed

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Section J

SPECIAL CONSIDERATIONS

* Skin allergy in animals
* Skin allergy in pregnancy
* Skin allergy and sports
* Skin allergy and airways disease
* Skin allergy in children

1 SKIN ALLERGY IN ANIMALS

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KEY MESSAGES

- Atopic dermatitis is the most common canine skin allergy and (in contrast to cats) well defined in dogs
- Food-induced atopic dermatitis is commonly seen in dogs and cats, but unusual in horses
- Urticaria due to environmental allergies is more common in horses
- Antihistamines and allergen immunotherapy are more commonly used as treatment for skin allergies in animals than in humans

Although many animal species can show pruritus of presumed allergic origin, most of the scientific research has been focussed on dogs and horses. In dogs, atopic dermatitis is a common inflammatory skin disease and may be triggered by food or environmental allergens. The pathogenesis is very similar to that of human atopic dermatitis with an initial exaggerated Th2 response, increased concentrations of allergen-specific IgE and in chronic cases an increased Th1 response.

The majority of dogs have extrinsic atopic dermatitis, intrinsic atopic dermatitis or (as it is called in dogs) atopy-like disease, which is seen in approximately 10-15% of the animals. Clinically, the disease is characterised by pruritus predominantly on the distal limbs, face and ears, although perianal and ventral pruritus also occurs. Subsequently, secondary excoriation and infections with bacteria, predominantly *Staphylococcus pseudintermedius*, and yeast, typically *Malassezia pachydermatitis* occur.

The disease is diagnosed by history, clinical signs and exclusion of differential diagnoses. Offending environmental allergens are identified with skin testing or serum testing for allergen-specific IgE. In contrast to human AD, allergen immunotherapy is an accepted and efficacious treatment for canine AD caused by environmental allergens. Food allergy is best diagnosed with an elimination diet for eight weeks consisting of a protein and a carbohydrate source never fed before.

If clinical signs improve, deteriorate upon rechallenge with the old food and improve again on the 'test' diet, the diagnosis is confirmed. Most dogs remain on a restricted diet for life. Table 1 outlines treatments for skin allergies in animals. The dense hair coat of animals makes creams and ointments less practical than in humans. Although dogs may develop urticaria due to environmental or food allergens, "hives" are much more common in horses and together with non-lesional pruritus are the most common presentations of skin allergy.

In horses, food allergy is very rare; reactions to environmental allergens such as mould spores, pollens or storage mite predominate. The diagnostic approach is similar to that in the dog. There are no current published reports on cyclosporine and oclacitinib in horses, possibly because they are cost-prohibitive treatments Antihistamines are commonly used for allergic skin disease in the horse with good to moderate success, more severe cases will receive glucocorticoids. As in the dog, allergen immunotherapy has been used successfully in horses with chronic disease due to environmental allergies. In

TABLE 1

Treatment for skin allergies in animals

Treatment	Drug type	Dose	Species	Efficacy	Adverse effects
Allergen immunotherapy		Details see [2]	Dog, cat, horse	Good	Rare anaphylactic reactions
Prednisolone	Glucocorticoid	0.2-1 mg/kg PO q 48h	Dog, cat, horse	Excellent	Polyuria, polydipsia, polyphagia, lethargy, comedones, skin and muscle atrophy, secondary infections, phlebectasia, calcinosis cutis
Cyclosporine	Calcineurin-inhibitor	5-7 mg/kg PO q 24-72h	Dog, cat	Excellent	Diarrhoea, vomiting, gingival hyperplasia, papillomatous eruptions
Oclacitinib	Janus-kinase-inhibitor	0.4-0.6 mg/kg PO q 24h	Dog	Excellent	Secondary infections, histiocytomas
Lokivetmab	Monoclonal anti-IL-31-antibody	1-2 mg/kg SC q 28d	Dog	Excellent	Lethargy
Hydroxyzine	Type 1 histamine receptor antagonist	2 mg/kg PO q 12h	Dog, cat, horse	Moderate	Sedation, teratogenicity
Chlorpheniramine	Type 1 histamine receptor antagonist	0.4-1 mg/kg PO q 12h	Dog, cat, horse	Moderate	Sedation
Dimetinden	Type 1 histamine receptor antagonist	0.1 mg/kg PO q 12h	Dog, cat	Moderate	Sedation
Pentoxifylline	Xanthin derivative	15-25 mg/kg PO q 12h	Dog, horse	Moderate	
Essential fatty acids		50 mg/kg PO q 24h	Dog, cat, horse	Moderate	Diarrhoea

cats, pruritus leading to alopecia without lesions, severe self-traumatised dermatitis, miliary dermatitis (multiple crusted papules) and eosinophilic granuloma may all be seen with environmental or food allergies. Tablet administration is much more difficult in the cat than in dogs or horses.

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2 SKIN ALLERGY IN PREGNANCY

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INTRODUCTION

EPIDEMIOLOGY OF ATOPIC AND ALLERGIC SKIN DISEASES IN PREGNANCY

Mast cells are present in the placenta, and their mediators, such as histamine have physiologic functions before and during pregnancy (implantation of blastocyst, myometrial contractions). Pregnancy and labor present a number of stressors that trigger mast cells, posing a higher risk in settings of elevated mast cell numbers like in mastocytosis. As a result skin eruptions (urticaria, pruritus, flush, dermatographism) and systemic symptoms (flush, abdominal pain, anaphylaxis) may occur. In contrast, the *anaphylactoid syndrome of pregnancy* is caused by amniotic fluid embolism in the delivering mothers´ circulation. An examination of 45 births to women with mastocytosis showed a preterm birth rate of 6.6% comparable to the mean European rate.

Overall, itchy dermatoses affect 50-90% of pregnant women, among them atopic eczema in 30-50%. Differential diagnoses include atopic eruption of pregnancy (AEP), polymorphic eruption of pregnancy (PEP), pemphigoid gestationis (PG) and intrahepatic cholestasis of pregnancy (ICP).

KEY MESSAGES

- AD mostly worsens during pregnancy, requiring special attention of the skin barrier and prevention of itch
- Steroids should be given topically, and the choice of antihistamines is limited to chlorphenamine, cetirizine or loratadine
- In diagnosis of pregnant allergics and atopics the risk for mother and child have to be considered. Allergen exposure of sensitized pregnant women - natural, diagnostic or therapeutic - should be avoided due to a potential risk of side effects for two individuals

PREGNANCY AFFECTS THE HEALTHY SKIN AND CAUSES A TH2 IMMUNE BIAS

Immunological, metabolic, vascular, endocrinological and physiological changes during pregnancy may affect the skin. The latter include hyperpigmentation, *striae cutis distensae*, *pruritus gravidarum*, changes in hair and nail thickness, and functional changes of eccrine glands (increased sweating), apocrine glands (reduced sweating) and sebaceous glands (increased activity). The immune balance tips from Th1 to Th2. For tolerance towards the fetus, the placenta produces higher levels of IL-4 and IL-10, and lower levels of IL-12 and IFN-γ. As a result, Th1-driven skin diseases like psoriasis may improve, but Th2-associated disorders like atopic eczema tend to worsen, and due to impaired cellular immunity, the risk of skin infections is higher (Figure 1).

CHANGES IN ATOPIC DERMATITIS DURING PREGNANCY

"Atopic eruption of pregnancy" is most common and occurs in 50% of atopic dermatitis (AD) patients mainly in the first trimester: 20% of women show exacerbation of pre-existing eczema, 80% are affected for the first time or after a long symptom-free period. Filaggrin-mutations enhance the risk for AD flares in pregnancy. The fact that atopic eczema either persists or worsens during pregnancy may be attributed to reduced treatment before or during

Figure 1 Short overview of the Do´s and Don'ts for pregnant allergics. The Th2 bias favours AD and related dermatoses. Any manipulation may affect mother and child, with a risk of fetal malformations, or anaphylaxis especially in patients with preexisting allergies. *) Even though for most biologics the evidence is sparse, for omalizumab safety data are available for pregnancy from the EXPECT study [13] (Fotolia.com©Reicher)

pregnancy. In 10,668 birth-giving women with AD, most reported reduced usage of topical corticosteroids and ultraviolet therapy for AD as compared to before pregnancy. A positive association of maternal AD was found with premature rupture of membranes (PROM) of the amniotic sac, and for neonatal septicaemia, probably due to skin barrier defects and colonization with *Staph. aureus* in AD.

DIAGNOSIS OF ALLERGY IN PREGNANCY

Skin prick testing is obsolete in pregnant allergics and poses a risk for mother and child (Figure 1). Despite the fact that no harmful effects of patch testing during pregnancy are known, most physicians deter testing as a general precaution. Moreover, due to immunological and/or hormonal changes during pregnancy, results of skin tests may not be reliable. However, if an occupational allergy is suspected, patch testing can be done with a limited number of allergens. The diagnosis of allergy in pregnant women should thus focus on medical history, determination of specific IgE, and in case of urticaria, tryptase levels. In unclear cases of skin disorders referral to skin biopsies and immune-histochemical analysis is recommended.

MANAGEMENT OF ATOPIC SKIN DISORDERS AND ALLERGY DURING PREGNANCY - THE DOS AND DON´TS

Pregnant women with AD should avoid hot showers and getting sweaty, which are important triggers of itch, while cool compresses reduce it. For the same reason irritants like scented products, chemicals, metals, wool, pet dander, juices of meat and fruits etc. should be avoided. Scratching of the skin should be avoided especially to prevent secondary bacterial infections.

To preserve barrier function and minimize necessity of specific treatment, pregnant women should regularly apply sufficient emollients (including urea or glycerol).

Limited availability of studies leaves pregnant AD patients with insufficiently treated skin symptoms, often highly pruritic and therefore causing considerable distress. Non-irritant non-synthetic clothes may help. In cases where avoidance strategies fail, mild to moderate corticosteroids can safely be applied topically (Figure 1). The usage of potent and very potent topical corticosteroids, especially when reaching a high cumulative dose over pregnancy, can lead to low birth weight. Usage of the lowest dose of anti-histamines chlorphenamine, cetirizine or loratadine is recommended, their intake in the first trimester was not correlating with major malformations or other fetal defects. Hydroxyzine is contraindicated in early pregnancy. Data on applicability of dupilumab and other biologics are not available yet. Leukotriene receptor antagonists are safe in pregnancy.

The treatment of mastocytosis in pregnancy involves avoidance of triggers, prophylactic antihistamine therapy, and corticosteroids, further antihistamines and epinephrine if needed. Anaphylaxis in pregnant mastocytosis patients goes along with massively elevated diamine oxidase levels.

Chronic spontaneous urticaria (CSU) most often improves during pregnancy, but data from the EXPECT study indicate that omalizumab may be used for antihistamine-resistant urticaria also in pregnancy.

Allergen-specific immunotherapy (AIT) should not be started *de novo* in pregnancy. Continuing ongoing AIT during pregnancy seems safe.

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3 SKIN ALLERGY AND SPORTS

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KEY MESSAGES

- Exercise and Sports activity are important triggers for skin allergy syndromes
- In Exercise-Induced Urticarias, performing the correct diagnostic work-up is fundamental for differential diagnosis
- Exercise-Induced Urticaria may be a prodromic symptom for Exercise-Induced Anaphylaxis
- WADA anti-doping regulations must be always taken into consideration when treating professional athletes

INTRODUCTION

Skin Allergy manifestations in sports practicers are usually related to the use of sports equipment, linked to specific environmental situations, may be presentations of induced urticarias or related to specific allergic syndromes whose symptoms are exacerbated or triggered by exercise, such as food-dependent exercise-induced anaphylaxis.

CONTACT DERMATITIS

The increasing use of latex and neoprene equipment in various sports has been associated to an increased incidence of contact dermatitis (CD). CD due to athletic tapes (mainly linked to formaldehyde allergy) may occur in various disciplines. Thiourams and mercaptobenzothiazole seem to be the haptens more frequently involved. In footballers, Lichenoid photodermatitis are possible.

In swimmers, there have been descriptions of CD arising from phenol-formaldehyde resin and benzoyl peroxide contained in swimming goggles, or from diphenylthiourea or other substances in wet suits.

Athletes that practice water sports may face hypersensitivity reactions, like the "swimmer's itch", a cercarial dermatitis due to tiny larvae of Schistosomatidae worm, or the so-called "seabather's eruption", a form of highly-pruritic dermatitis caused by Cnidaria larvae (phylum of the Jellyfish and similar animals). It is also worth noting that Jellyfish stings, very common in marine sports practices, can lead to sensitization to Poly(γ-glutamic acid) (PGA), common allergen of a traditional Japanese food called "natto" (fermented soybeans), therefore leading these athletes to a high risk of anaphylactic reactions after ingestion of this food or of jellyfish itself.

Finally, it must be noted that sweating and cutaneous dehydration linked to physical activity, and the frequent use of detergents, may worsen the clinical picture (also with bacterial superinfection) in subjects with atopic eczema.

Treatment of these forms, beside avoidance of the trigger, is usually topic, with corticosteroids and antihistamines. Systemic treatment with the same medications is possible in more serious clinical pictures and, as in the other skin allergies, World Anti-Doping Agency (WADA) regulations for professional athletes must always be considered.

URTICARIA AND SPORTS

Six main forms of urticaria may be related directly to sports activity and exercise, and all are physical urticarias.

Delayed pressure-induced urticaria is characterized by a deep and painful pomphoid reaction which

may develop 3-12 hours after a pressure stimulus, and which can last up to a day. In general, it affects body areas under an increased pressure (the buttocks of a cyclist, the hands of athletes who use their hands in their sports, or even in areas where a particular equipment with belts, straps, or slings leads to an increased pressure).

Cold-induced urticaria may occur in winter sports athletes and, in general, with low environmental temperature. The clinical picture can be serious, sometimes overlapping with exercise-induced anaphylaxis.

Solar urticaria may affect the many athletes directly exposed to the sunlight. Symptoms are erythema and wheals within 5 min of exposure to rays of a wide range of length, which may vary individually. Heat urticaria can be a differential diagnosis.

Factitious Urticaria, known also as "dermographism", may develop during the movements associated with sports activitity. It must be differentiated by simple dermographism because also pruritus, and not only wheals, is present.

Cholinergic urticaria is characterized by itchy pin point-sized, short lived wheals with pronounced surrounding flare reactions. which in sports may occur in response to increase core body temperature due to physical exercise or also to passive warming or emotional stress. Usually, to allow a differential diagnosis with other Exercise-induced Urticarias, a rise of 1.0°C of body temperature by a passive warming, sitting for up to 15 min in a bath full of water at 42°C should be performed after a positive exercise test. Recently, also pulse-controlled ergometry showed good sensitivity and specificity as a diagnostic tool in a small group of patients.

Aquagenic urticaria is provoked by the simple contact of the skin with water at body temperature. The lesions resemble those of cholinergic urticaria, can appear immediately or 30 min-1 h after contact with water. Usually, lesions regress spontaneously after circa 30 min.

Treatment of all these forms is usually based on antihistamines and systemic corticosteroids. In some case reports, omalizumab treatment has been proven successful.

EXERCISE-INDUCED ANAPHYLAXIS

Finally, exercise-induced urticaria may be part of the clinical picture of an exercise-induced anaphylaxis (EIAn), which may lead to serious consequences, thus careful clinical observation of the patient with EIU and a proper diagnostic workup is strongly recommended. In fact, EIAn is only in the minority of cases caused by exercise alone, and in the vast majority of patients may reflect a food allergy with a subclinical Food-Dependent Exercise-Induced Anaphylaxis (FDEIAn), in which exercise as well as other cofactors (e.g. non-steroidal anti-inflammatory drugs, alcohol, infections, stress, menstruation, extreme temperatures extreme) can elicit symptoms in patients otherwise tolerating the food. The most common food causing FDEIAn when followed by exercise or other cofactors is wheat, but a lot of eliciting foods and food lipid transfer proteins have been described.

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4 SKIN ALLERGY AND AIRWAYS DISEASE

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KEY MESSAGES

- Skin allergy is not only confined to the skin, but is a systemic disease with strong impact on the airways
- Early-onset AD and the its severity determines the development of other allergic diseases in later life
- Dysfunctional epithelial barrier with reduced junctional integrity and impaired innate defence allows the penetration of allergens and microbes, predisposes to allergen sensitization and leads to activation of systemic type 2 responses)
- The exposure to diverse bioparticles and microbiota through defective epidermal barrier affects the local tolerance
- Prophylactic measures including allergen immunotherapy and regular emollient use can be taken however solid evidence of efficacy is lacking

INTRODUCTION

Skin allergy is often comorbid with asthma, allergic rhinitis or food allergy. There is a link between early-onset AD and the development of other allergic diseases in later life. In addition, the severity of AD determines the development of allergic manifestations. Several prospective birth cohorts have shown associations between early-onset AD and development of asthma and allergic rhinitis in school age. The importance of allergic sensitization has been stressed. It was found that children with AD and allergic sensitization had an increased risk of food allergy, asthma and allergic rhinitis compared to non-sensitized children without AD.

Mechanistic insights into the pathways that may be responsible for triggering the progression from skin allergy to allergic airway disorders have been provided (Figure 1). In allergic disease, epithelial dysfunction can be found before the development of symptoms. Such conditions are characterized by impaired homeostatic balance with loss of differentiation, reduced junctional integrity and impaired innate defence.

Recent evidence demonstrates the efficacy of early interventions targeted at AD and airway disease.

Thus, skin allergy can be considered as not only confined to the skin, but in fact constitutes a systemic allergic disease with strong impact on allergic airway disease.

SKIN ALLERGY AND AIRWAY DISEASE - EVIDENCE FROM CLINICAL STUDIES

AD is often the first manifestation of atopy which originates in early infancy. In atopic children, adolescents, and adults, allergic symptoms may evolve according to a predetermined scheme, with the progression from atopic dermatitis (AD) to allergic rhinitis (AR) and asthma called the atopic march. However, recently it has been shown that the complete manifestations of the atopic march might appear in less than 10% of AD patients.

The atopic predisposition represents a major risk factor for developing all atopic diseases. Transcutaneous IgE-sensitization may precede airway sensitization and predict the development of allergic diseases including allergic rhinitis, and asthma.

The development of allergic airway diseases in AD patients is de-

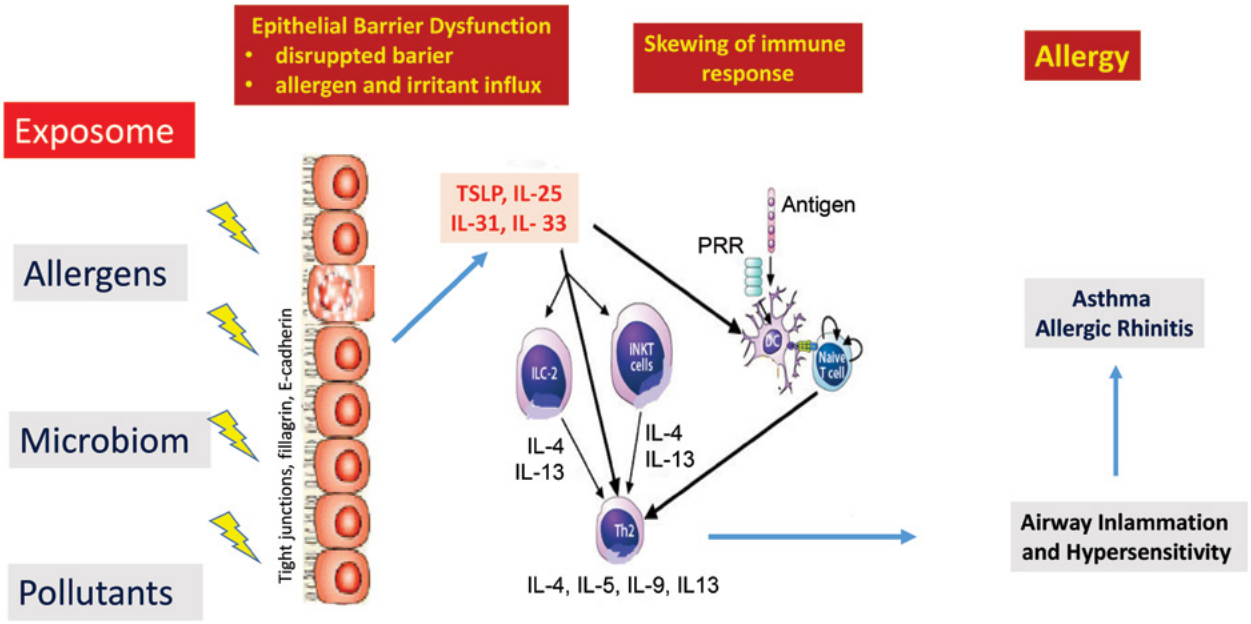

Figure 1 Epithelial barrier dysfunction and development of systemic sensitisation and allergic disease. Various exposome factors affect both innate and adaptive immunity and skew towards type 2 response predisposing to systemic allergic disease

termined by the age of AD onset and its severity. In the MACS study high-risk infants with early-onset persistent AD had a 3-fold risk of developing asthma and allergic rhinitis in later childhood, compared to children with late-onset AD after 2 years of age. More than 60% of children with severe AD before 3 years of age developed asthma by age 7, compared to only 20% of those with mild AD. AD was also associated with more severe asthma and a greater persistence into adulthood.

GENETIC BACKGROUND

Shared asthma, hay fever and AD immune-related gene variants were identified in a GWAS study. These allergic conditions seem to share genetic risk loci or overlaps between asthma and AD that result in dysregulation of immune-related genes. Novel genetic loci (rs9357733 located in EFHC1 on chromosome 6p12.3 and rs993226 between TMTC2 and SLC6A15 on chromosome 12q21.3) might be specific for the AD-to-asthma atopic march phenotype. A Kinesin family member 3A (KIF3A) genetic variant was also found to be associated with AD-asthma comorbidity (reviewed in 1).

MECHANISMS OF PROGRESSION FROM SKIN ALLERGY TO ALLERGIC AIRWAY DISORDERS

Pathways responsible for progression from the sensitization in the skin and skin barrier dysfunction to allergic airway disorders have been described. The dysfunctional epithelial barrier, which allows the penetration of allergens and microbes, leading to activation of type 2 response is a hallmark of allergic disease. Impaired skin barrier predisposes the epicutaneous allergen sensitization.

Barrier loss can result from defects in tight junction proteins, protective antiproteases, structural elements such as filaggrin in the skin, transport of ions, protons, water or antimicrobial materials and activation of sensory nerves.

The inflammatory responses induced by AD are manifested by activation of type 2 immune-response characterized by IL-4, IL-13, IL-25, IL-33 and TSLP production. TSLP is associated with systemic responses and significantly contributes to the development of airway disease. TSLP is an IL-7 related cytokine that is expressed predominantly in skin keratinocytes, pulmonary airways and intestinal epithelium. Intradermal administration of TSLP together with OVA, in mice, leads to an AD-like skin inflammation with epicutaneous OVA sensitization, and results in an allergic asthma-like phenotype upon airway OVA challenge. In a murine model overproduction of TSLP by AD skin induced airway sensitization and response to house

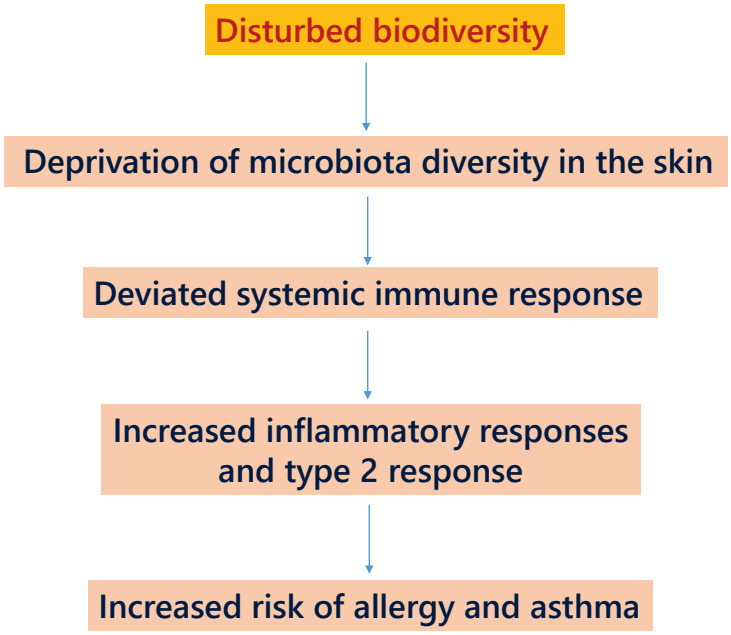

Figure 2 Disturbances in biodiversity are crucial for defective immune response and development of chronic inflammatory diseases including systemic allergic disease

dust mite (HDM) in sensitized animals. Epicutaneous sensitization without an structurally impaired skin barrier might also play a role. IgE-mediated wheat protein allergy was also observed in previously healthy individuals after chronic usage of agents affecting the epithelial integrity.

BIODIVERSITY AND MICROBIOTA

According to biodiversity hypothesis, the contact with natural environment enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders. Microbial diversity plays a role in health and disease. Development and maintenance of mucosal tolerance seem to depend on environmental exposure to diverse bioparticles and microbiota. On normal skin, diversity of the microbiota is high, while exacerbation of e.g. atopic eczema calls invasion of the opportunistic Staphylococcus aureus. Efficient interaction between Toll-like receptors with the ligands of microbes and bioparticles enhances normal mucosal function and prevents from allergen-specific Th2 cytokine production. This might have an impact on the development of allergic airway disease (Figure 2).

PREVENTIVE MEASURES

Several primary prevention strategies for asthma and allergic rhinitis have also been investigated. These include regular emollient use, HDM avoidance in early life and prophylactic immunotherapy in sensitized children. None, however, have shown sufficient evidence for adoption into routine clinical practice yet.

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5 SKIN ALLERGY IN CHILDREN

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KEY MESSAGES

- Although food allergy might exacerbate AD, introduction of a restrictive diet should always be correlated with the clinical history and if needed, a double-blind-placebo-controlled food challenge
- The most common cause of acute urticaria in children is infection, particularly viral infection, even if a drug is taken concomitantly
- In case of benign exanthema or delayed urticaria (no danger sign) during a betalactam treatment, skin tests can be skipped before the DPT
- Drug provocation test in children with suspicion of NSAID hypersensitivity if of major importance

The most common manifestations of skin allergy in children are eczema, urticaria/angioedema and exanthemas. Some specific aspects are important to take into account when taking care of children with a suspicion of skin allergy.

Atopic dermatitis (AD) is common in children with an estimated incidence ranging between 15% and 30%. Although still controversial, evidence in the literature exists on the role of allergy in a subgroup of patients with AD. It has been found that infants and young children with AD are commonly sensitized to food allergens (30-80%), but these sensitizations are not always clinically relevant. Only a small proportion has a confirmed food allergy, which might be responsible for 2 types of skin manifestations: urticaria/anaphylaxis and food-exacerbated AD. The rate of food-exacerbated AD increases with the severity of eczema, and typically reaches one third of patients with the most severe form. Elimination of the incriminated food might lead to significant clinical improvement. However, introduction of a restrictive diet should not be based only on a positive skin test or specific IgE, but always correlated with the clinical history and if needed, a double-blind-placebo-controlled food challenge. Aeroallergens might play a role in subgroup of older children and adults, although less data are available. Contact dermatitis is less common in children compared to adults. However, it is important to consider this entity in older children, particularly those with AD.

Acute urticaria (associated or not with other symptoms of anaphylaxis) is common in pediatrics and might be induced by an allergy to foods, drugs or hymenoptera venom. However, the most common cause of urticaria remains infection, particularly viral infection, as is the case for exanthemas. Viral-induced urticaria or exanthema might mimic a drug allergy. When a beta-lactam is taken concomitantly to the occurrence of the rash, it has been found that only 10% of the patients will have an allergy confirmed by a positive drug provocation test. In children, it has been demonstrated that in case of benign exanthema or delayed urticaria (no danger sign) during a betalactam treatment, skin tests can be skipped before the DPT (Figure 1). It is also important to recognize NSAIDs as one of the most common causes of drug hypersensitivity in the pediatric population. Urticaria is the most common manifestation of NSAID hypersensitiv-

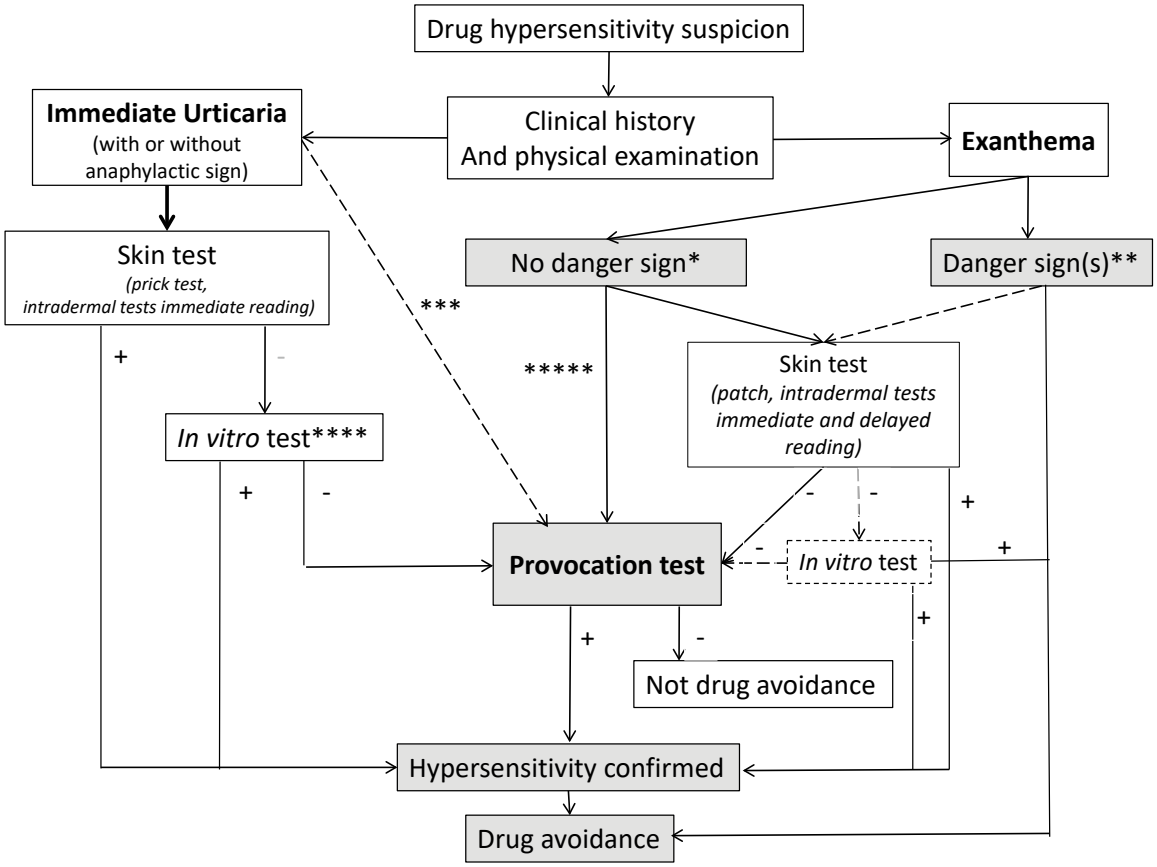

Figure 1 Management of children with suspicion of drug hypersensitivity (adapted from (4)). *Non severe uncomplicated exanthemas. ** This category include more severe exanthemas, such as those with high extent and density of skin lesions and long duration, complication or danger signs. It includes also acute generalized exanthematic pustulosis, drug reaction with eosinophilia and systemic symptoms, Stevens Johnson Syndrome or toxic epidermal necrolysis. In specific cases, skin tests may be considered for identification of culprit among several used drugs. ***For NSAID and non-BL antibiotics, the diagnostic value of skin tests is not well defined. In case of isolated urticaria, a DPT can be performed directly. **** Validated in vitro tests recommended before skin tests if history of severe reaction or if skin tests are not possible or refused. They may confirm hypersensitivity only together with convincing history and/or other tests. Practically, specific IgE are mainly used for suspicion of hypersensitivity to BL antibiotics. ****** In the pediatric population, it has been shown that a drug provocation test can be performed directly, without skin test before, in children with a non severe uncomplication exanthemss. If there is any doubt, skin tests should be performed before drug provocation test

ity and isolated facial angioedema is a pathognomonic manifestation. Recent data also highlight the importance of a DPT in children with suspicion of NSAID to confirm a hypersensitivity in around 20% of patients (Figure 1).

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Section K

COMPREHENSIVE GLOBAL STRATEGY FOR THE MANAGEMENT OF SKIN ALLERGY

* Burden of skin allergies as non-communicable diseases
* Patient organizations
* The role of pharmacists
* Dietary Considerations
* Role of allergy school and education
* Allergic skin disease: a global burden

1 BURDEN OF SKIN ALLERGIES AS NON-COMMUNICABLE DISEASES

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INTRODUCTION

The skin is like no other organ affected by a multitude of allergic diseases and pathophysiologies. In addition, systemic allergic diseases often go along with skin symptoms, urticaria may herald anaphylaxis. The most important allergic skin diseases are atopic eczema, urticara/angioedema, allergic contact dermatitis and cutaneous drug eruptions; they also can occur as non-immune variants ("intrinsic" or "idiopathic"): While some decades ago skin allergies were regarded as a disease of the "rich" western societies, this is past: we find severe forms of atopic eczema, urticaria and contact dermatitis in all parts of the world.

Burden of disease has to be considered specifically for the individual suffering from skin allergies (Figure 1). Besides mortality and economic costs, functional impairment in e.g. chronic hand eczema with work loss, it is the subjective symptoms like pain and especially itch, which can be excruciating and lead to suicide ideation. Also disfigurement plays a role. In spite of all modern developments of a tolerant society, the social attitude towards patients with skin affections is still archaic in most

KEY MESSAGES

- Skin allergies represent a major public health problem with a substantial socio-economic and individual burden worldwide
- Patients with skin allergies are suffering more than what would be acceptable and at the same time need a much better access to affordable health care
- There is a high unmet need for an increased awareness among physicians and other healthcare professionals but also policy makers and the general public
- Worldwide research on skin allergies has to be promoted and affected patients must be granted access to better and affordable health care

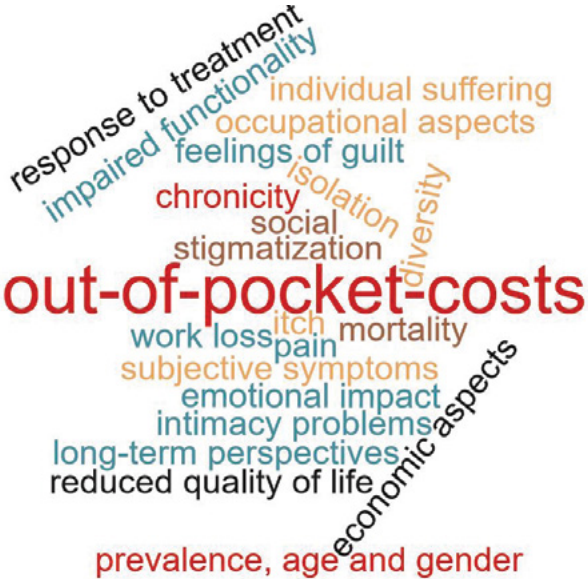

Figure 1 Burden of disease in skin allergy and individual suffering

TABLE 1

Prevalence of allergic skin diseases			
Atopic eczema / atopic dermatitis	**Urticaria / angioedema**	**Allergic contact dermatitis**	**Cutaneous drug eruptions**
10 – 20 % in childhood	20 - 30% acute urticaria	10 – 20 % Contact allergy	10 – 20 % of all hospitalized patients
2 – 5 % in adults	2 - 5% chronic urticaria	6 – 10 % Chronic hand eczema	7 % of the population
		30 – 40 % of notifications for occupational disease	

societies of the world and leads to social isolation and stigmatization. A further aspect of burden is the long-term outcome, namely the chronicity and poor response to therapy. Besides symptomatic treatment there is no "cure"; the disease will relapse sooner or later. This leads to a permanent anxiety affecting quality of life.

A global survey has studied the years lost due to disability for a variety of diseases and found skin disease to rank as Nr 4 after "low back pain", "major depressive disease" and "iron-deficiency anemia". Asthma was found to rank as Nr 15. One third of skin diseases leading to 400 – 600 years lived with disability (YLD) / 100 000 are conditions like eczema, urticaria and itch.

PREVALENCE OF SKIN ALLERGIES

One major aspect describing the burden of a disease for society is the prevalence of the condition. Allergic skin diseases belong to the most common non-contagious inflammatory diseases. From many epidemiological studies, one can safely state that around 20% of a population are affected at least once in their lifetime by skin allergy (Table 1) which is probably underestimated. Regarding gender issues in the adult population, females are more often affected than males. In 15% of population contact allergic reactions are found both in patient cohorts from dermatology departments and in the general population representing some of the most common occupational diseases. Apart from problems in occupational life, patients with contact allergy are severely impaired in their daily life by e.g. allergy to fragrances, preservatives in ointments ore cosmetics.

INDIVIDUAL SUFFERING

Due to the specific characteristics of individual suffering in skin allergy, there is tremendous impairment in QOL for affected people. Some studies have shown that in the impairment of quality of life atopic eczema ranges between myocardial infarction, apoplexia (stroke) and Morbus Parkinson (Figure 2).

The degree of individual suffering was recently studied in ca. 1200 adult patients with atopic eczema from 9 European countries who were all well treated according to dermatological standards. More than half of the patients were suffering remarkably and were emotionally burdened with feelings like "trying to hide the eczema", "feeling guilty about eczema", "problems with intimacy" and more. Of persons actually suffering from severe atopic eczema, 88% stated that their eczema at least partly compromised their capacity to face life.

PROBLEMS IN MANAGEMENT

A further problem in skin allergy is the lack of causal treatments except avoidance recommendations after allergy diagnosis. Therefore, allergy diagnosis down to the identification of the eliciting substance at the molecular level is crucial in skin allergy. Contrary to respiratory allergy or insect venom anaphylaxis there is no routinely available procedure of allergen-specific immunotherapy or tolerance induction in skin allergy. Another trait of allergic skin diseases is the strong psychosomatic influence, most notably evident by stress-induced exacerbations of symptoms. There also seems to be a marked degree of "suggestibility" which may explain the high rates of positive placebo responses in clinical trials. The use of unproven or non-evidenced "alternative" procedures in diagnosis and therapy is common. Therefore, educational programs such as "Eczema School" are important.

FUTURE OPTIONS

New therapeutic options have been developed with biologics specific against Interleukin 4 or IL13,

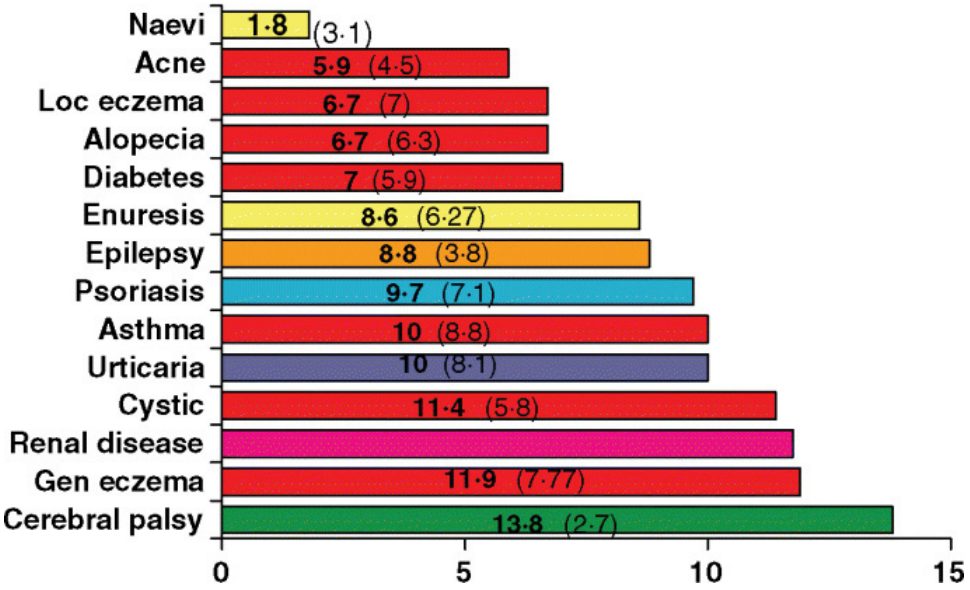

Figure 2 Quality of life impairment in children with several diseases and atopic eczema (according to Beattie et al. Br J Dermatol 2006)

IL 31, TSLP and other cytokines. Also small chemicals as jak-kinase or phosphodiesterase 4-inhibitors show promising effects. Anti-IgE has become standard in treating chronic spontaneous urticaria. In the field of cutaneous drug eruptions - due to lack of controlled clinical trials - there is still a controversy with regard to the use of IVIG, glucocorticoids, immunosuppressive drugs or biologics in the acute treatment of SCAR.

CONCLUSIONS

Skin allergies represent a major public health problem leading to a high socio-economic and individual burden. Patients with skin allergies are suffering more than what would be acceptable. There is a need for increased awareness among physicians and other healthcare professionals but also policy makers and the general public. Efforts should be taken to support research in the field and at the same time open the access to better and affordable health care for affected patients.

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2 PATIENT ORGANIZATIONS

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KEY MESSAGES

- The role of PO in the journey of patients suffering from skin allergy is to provide support and information, allowing them to increase their allergy management and prevent exacerbations
- Skin affections are recurrent and to avoid therapeutic failure, healthcare and PO work closely together to increase patient's self-management
- The work of PO contributes to prevention policies and to promote public health – a role usually played by governments

From the first patient organisation to nowadays, evolvement of these non-profit organisations has constantly been developing to become a key partner in healthcare. Patient organisations (PO) assume an advocacy role and support the interest of their members in the public and political domain. PO help patients with skin allergy to understand their condition and to encourage and enable them to deal with their everyday lives.

The role of PO in the journey of patients suffering from skin allergy is to provide support and information, allowing them to increase their allergy management and prevent exacerbations. Many PO offer useful information, based on medical and scientific recommendations, in printed version, but also through online media such as websites, social media and mobile apps. Some PO offer also phone services, with experts giving individual advice. Often, PO provide a safe and supportive environment for self-help groups to enable their personal exchange. Constantly evolving, all these services promote the "empowerment of patients", which plays a central role in the management and the prevention of the disease.

Skin affections are recurrent and to avoid therapeutic failure, healthcare and PO work closely together to increase patients' self-management. Therapeutic patient education (TPE) has shown positive results in maintaining treatment adherence, especially in the context of atopic dermatitis. Multidisciplinary teams of healthcare professionals, such as dermatologists, allergists, nurses, dieticians, psychologists in collaboration with PO, join their expertise to maintain treatment adherence. Patients with skin allergy often suffer from other allergic reactions, which in turn involve skin manifestations as well. In skin allergy not only the skin condition has to be considered, but also the psychosocial burden (e.g. stigmatisation, sleep disorder, psychological disorders). At the interface between healthcare and patients' needs, PO are key partners for the coordination and the realisation of TPE. All these opportunities give patients the chance to improve their quality of life.

Patient organisations contribute to raise the awareness of the lay audience about a particular disease. The work of PO contributes to prevention policies and to promote public health – a role usually played by governments. Unfortunately, the funding of PO's efforts is generally not covered by financial support of governments and PO are striving to keep costs to the minimum. Thus, the goal remains to maintain a high-quality support with optimal use of resources which calls for an even closer collaboration of all the important stakeholders.

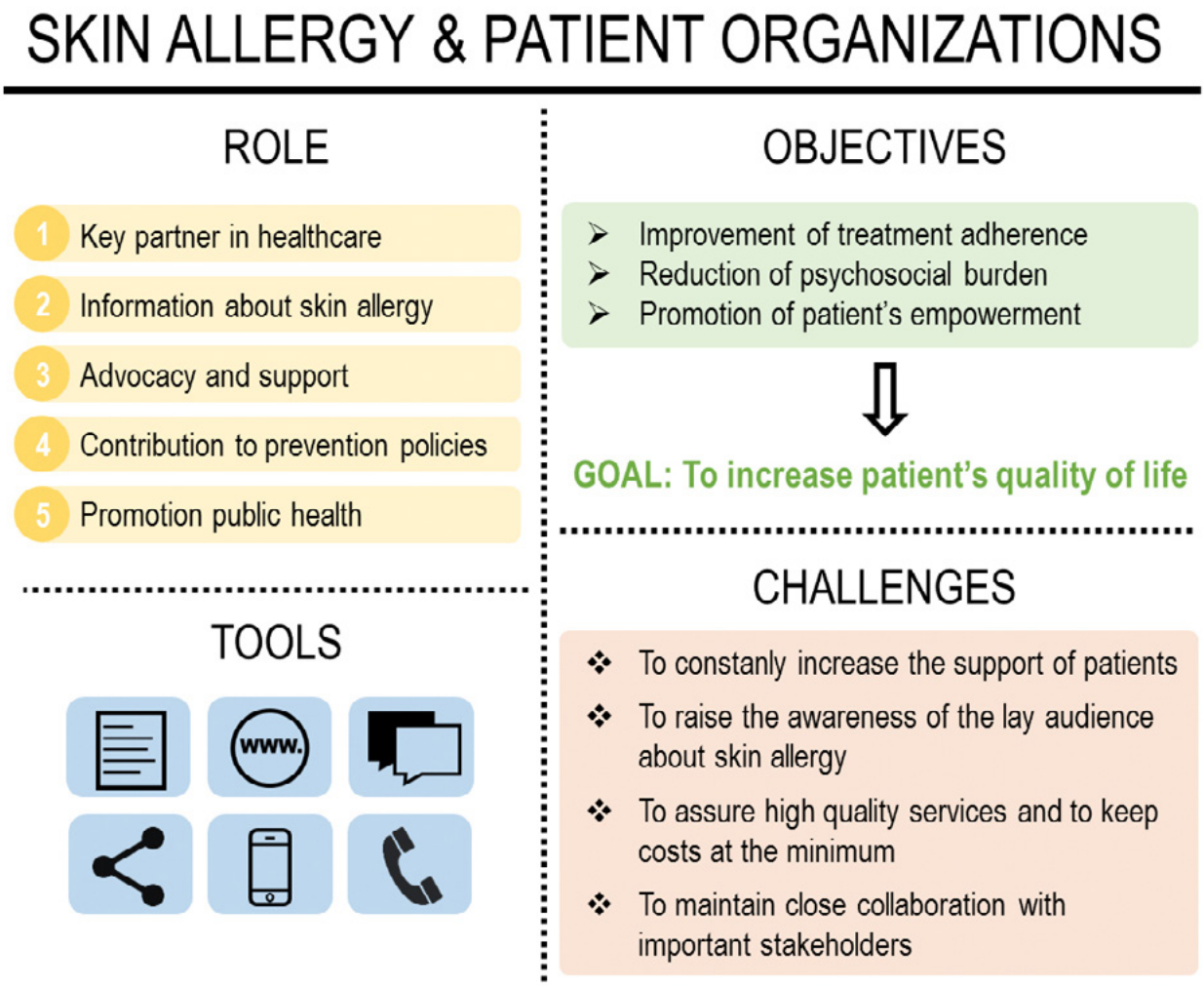

Figure 1 Overview of patient organisations' role, objectives, tools and challenges

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3 THE ROLE OF PHARMACISTS

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KEY MESSAGES

- Pharmacists should be actively involved in patient care as health professionals with a special focus on the safe and effective use of medication
- Pharmacists are often the first point-of-contact for patients with allergic skin diseases
- Pharmacists function as communicators between medical doctors, e.g. allergists and dermatologists, and patients
- Pharmacists can provide competent information on the basic therapy with emollients for patients with atopic dermatitis
- Pharmacists can take first actions in case of acute exacerbations before patients with allergic skin diseases may see a specialist

In the field of skin allergy, pharmacists play an important role as health professionals with a special focus on the safe and effective use of medication. Their field of action is broad and may be either in dispensing drugs as a community or hospital pharmacist, or in research, e.g. developing new drugs and sponsoring clinical trials. In particular, dispensing pharmacists function as communicators between medical doctors, e.g. dermatologists and allergists, other health care professionals and patients. Therefore, they should be actively involved in patient care (Figure 1). Pharmacists are often the first point-of-contact for patients with health problems (Figure 2). Here, we discuss specific roles for pharmacists in the field of skin allergy and the opportunities in which medical doctors, in particular allergists and dermatologists can synergistically interact with pharmacists.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting both children and adults. The therapeutic approach is stepwise and comprises a basic therapy aiming to restore the skin barrier for all patients. For most patients, a topical therapy is sufficient. Here, the pharmacist can give AD patients immense support.

Basic therapy comprises adequate skin care including the application of emollients, as well as cleaning with syndets or oil formulations. Emollients should be applied on both lesional and non-lesional areas. The choice of emollients depends on whether the lesions are acute (inflamed, oozing) or chronic (dry, scaly, lichenified). Moreover, it should also take into account the patients preferences, aiming to increase the adherence to therapy. The pharmacist can provide competent information on the formulation of the emollients, the content of moisturizers, preservatives and perfumes, and thus, the suitability of certain products. Basic therapy should be done as a daily routine and requires constant re-motivation of the patient.

As topical anti-inflammatory therapy, corticosteroids and calcineurin inhibitors are being used. Depending on legal regulation, pharmacists may dispense topical corticosteroids. For acute flares, a short-term application of topical corticosteroids is the first line therapy. Patients with chronic, recurrent and/or severe and extensive lesions should be referred to a dermatologist or allergist. The subsequent or alternating application of topical corticosteroids and topical calcineurin inhibitors

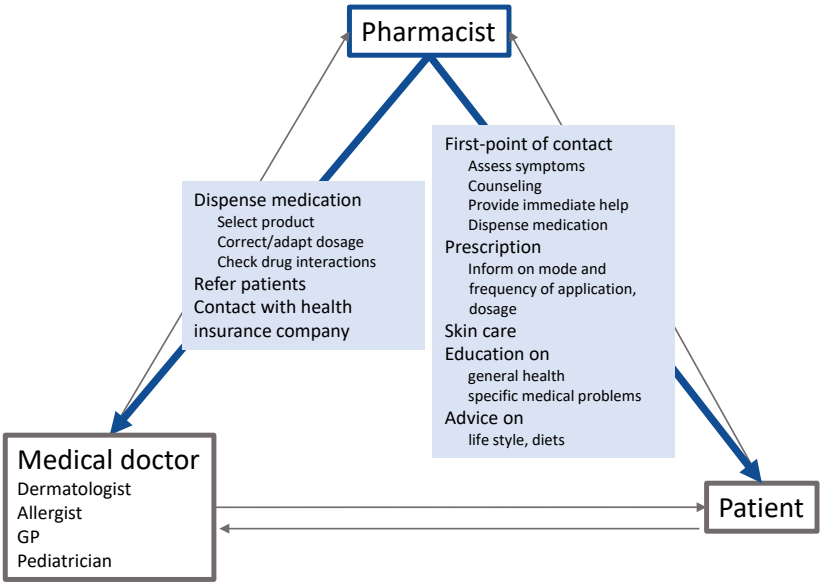

Figure 1 Pharmacists' role in patient care

can be an option for maintenance therapy. Here, the pharmacist can support the patients in implementing their individual treatment plan. As the pharmacist may be asked to comment on complementary methods and diets, they should assure that patients get adequate therapy while avoiding unnecessary restrictions.

URTICARIA

Urticaria is a mast cell-driven, histamine-mediated disease. Clinically, it manifests with an exanthema of hives accompanied by pruritus and, occasionally, angioedema. The individual lesion persists for minutes up to 24 hours, but new hives may appear. In most cases, urticaria is of the acute type that spontaneously resolves within 6 weeks. Chronic spontaneous urticaria persists for more than 6 weeks. Patients with an acute urticarial exanthema often approach the pharmacist as first contact. As acute urticaria is self-resolving, pharmacists can reassure patients about the benign course and dispense an antihistamine. According to current guidelines, non-sedating antihistamines are recommended that can be 4-fold higher dosed. However, in case of angioedema, an underlying allergic reaction or with untypical lesions that persist for more than one day, the patient should be referred to a specialist. There are number of differential diagnoses, e.g. urticarial vasculitis, eosinophilic dermatitis, acute febrile neutrophilic dermatosis (Sweet syndrome), bullous pemphigoid, that present with urticarial lesions.

CONTACT DERMATITIS

Contact dermatitis, in particular irritant contact dermatitis, is very common. As the disease course is often mild and lesions resolve upon avoidance of trigger factors, most affected individuals do not make use of medical consultation. Since in contact dermatitis, the skin barrier is damaged, emollients might be helpful. In case of severe and recurrent flares, the patients should be referred to a dermatologist for further diagnosis and treatment. To note, an important risk factor for chronic hand eczema is the delay of diagnosis and treatment. In order to identify a contact allergy, a patch test should be done. Here, pharmacists may educate patients no the use of skin care and protection products and dispense suitable ones.

DRUG HYPERSENSITIVITY

Both immediate and delayed drug hypersensitivity reactions often involve the skin. As the first action, the culprit drug(s) should be stopped. Mild forms can be treated with topical corticosteroids and antihistamines. However, to confirm the diagnosis and rule out internal organ involvement, and for drug testing, the patients should be referred to a specialist. If danger signs, e.g. painful skin, epidermal detachment, erythroderma, facial edema, and mucosal erosions occur, immediate action is required. For those patients requiring an emergency treatment set, pharmacists can provide much needed support for the correctly handling. It has been shown that in patients with a history of peni-

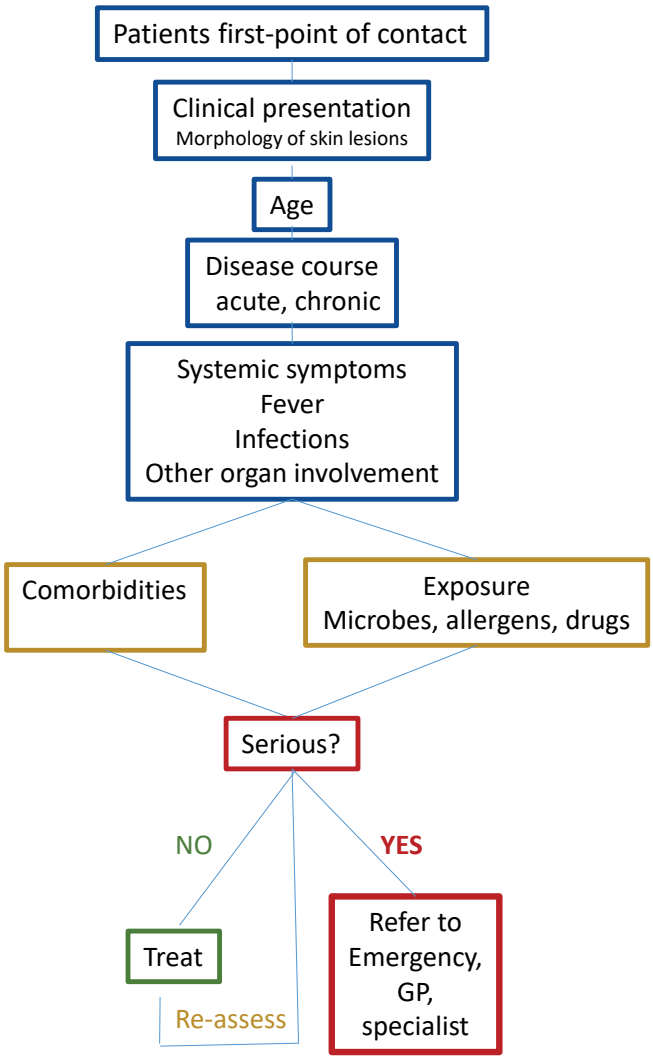

Figure 2 Decision algorithm for pharmacists: how to handle patients at first-point of contact

cillin allergy, a collaborative effort between allergists and pharmacists can increase β-lactam antibiotic prescriptions and lower non-β-lactam prescriptions.

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4 DIETARY CONSIDERATIONS

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KEY MESSAGES

- There should be no delay in the introduction of key allergenic foods into the diet of infants with Atopic Dermatitis
- One third of infants with Atopic Dermatitis can develop a food allergy, but dietary intervention must be supervised and foods reintroduced in a timely manner
- The nutritional consequences of food exclusion in those with Atopic Dermatitis may outweigh the benefits in those who do not have an IgE-mediated food allergy

Although there is little evidence that maternal nutritional supplementation prevents the onset of atopic dermatitis (AD) in offspring, it has been clearly demonstrated that key allergenic foods should be introduced into the diets of infants with AD in a timely manner. The delayed introduction of peanuts has been shown to increase the risk of the development of peanut allergy in children with AD. Food allergy affects approximately one third of those with AD, with cow's milk, hen's egg, peanut, soya, nuts and fish most commonly implicated in causality of symptoms. Where there is evidence of specific IgE sensitisation to foods, the removal of relevant foods may be beneficial, but dietary measures should only be instigated following a 4-6 week period of exclusion followed by oral food challenge. Since many children and adults with AD have high levels of specific IgE against many foods, it is vital that food exclusion is not undertaken without timely confirmation of its efficacy, since the removal of foods may provoke immediate food allergic reactions in people with AD who previously tolerated such foods. Specific IgE-guided exclusion may provide symptom relief for some individuals with AD, but popular dietary measures such as milk and/or egg exclusion, or more extreme measures such as elemental or few food diets, are not effective in the majority. The overemphasis of dietary exclusion, especially in young children, may have a highly detrimental effect on nutritional status. The removal of multiple foods from the diet can adversely affect nutritional intake and consequently growth, especially in young children. Thus the key to dietary management in AD is careful evaluation of sensitisation, rigorous exclusion and re-introduction, to ensure minimal impact on the developmental milestones (Table 1 and Figure 1). There is little convincing evidence that dietary supplements are useful in AD management, although mixed probiotic strains or combination of pre- and probiotics (Synbiotics) may be promising adjuncts to dietary management in the future. Although evidence might not support the efficacy of diet in the management of the majority of those with AD, most adults will have trialled food exclusion as a means of symptom improvement. It is therefore vital that dietary interventions are discussed with all patients and/or their parents/carers, and individualised dietary advice provided by a qualified dietitian, to improve patient-related quality of life and prevent adverse nutritional outcomes.

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TABLE 1

Nutritional Management of Food Exclusion

Food excluded	What other foods might need to be removed	Which nutrients may need attention	Substitute Foods
Cow's Milk	• Yoghurt • Butter and Margarine • Cheese • Buttermilk • Ice cream • Coffee creamers • Goat, sheep or buffalo milk products • Lacto-free milk and cheese • Other foods known to contain milk e.g. flavoured crisps, chocolate, cakes, biscuits, pizza, desserts	• Milk is a good source of energy, protein, calcium, B vitamins, iodine • Assess protein and energy intakes • Supplements of calcium and vitamin D may be necessary. • Iodine is an important trace element which should not be overlooked in children of all ages	**Milk substitutes:** • Birth – 2 years - Extensively hydrolysed formula/ Amino acid formula • 2-5 years - plant based milk substitutes with added calcium and energy e.g. Oat milk, nut milk, Coconut milk, (organic products may not contain added nutrients) • 5 years onwards: plant based milk substitutes including Rice milk **Other Foods** • Soy, coconut or nut-based yoghurts, cheese and processed milk free foods • Wheat products provide energy, protein, B vitamins and calcium. • Legumes and dark leafy vegetables provide B vitamins and calcium • Fish containing bones and tofu set with calcium compounds are also sources of calcium.
Eggs	Eggs in foods including: • Pancakes and waffles, • Bread crumbed or battered food • Cakes, pastries and desserts • Meat products e.g. beef burgers	• Eggs provide energy, protein, B vitamins, vitamin D • Although eggs are not so dominant in the diet as milk, they are present in many foods	• Meat, seafood and vitamin-D fortified milk all contain some of the nutrients missing from the diet • Beans and lentils are an important source of protein, especially for those following a vegetarian diet • Eggs replacement products, such as those made from algae, yeast, pea, soy and potato starch, provide the same properties as eggs in baked products but their nutritional value is lower
Peanuts, soy, and tree nuts	The following foods are more likely to contain nuts, peanuts or soy: • Bread • Chocolate bars and cereal bars • Breakfast cereals • Cakes, biscuits, pastries • Nut oils e.g. Walnut, hazelnut and almond oil • Unrefined or cold pressed peanut oil • Chinese, Indian and Thai food	• Legumes and tree nuts provide a variety of nutrients including energy, protein, fibre, omega 3 & 6 fatty acids, B vitamins (Folic acid, Thiamine, B6) Vitamin E, iron, calcium, selenium, magnesium, zinc • Vegans may need iron, calcium and B vitamin supplements	• Other nuts may be tolerated – this needs to be determined through oral food challenge or home reintroduction as required • Legumes, e.g. beans and lentils, will often be tolerated by peanut or soy allergic individuals • Seeds eaten in quantity will provide a similar nutrient profile to that of nuts • Fruits and vegetables can provide a healthy range of vitamins and minerals • Omega 3 fatty acids can be obtained through avocados and vegetable oils (except palm oil) • Soy lecithin and fermented soy products such as soy sauce or miso may be tolerated

Food excluded	What other foods might need to be removed	Which nutrients may need attention	Substitute Foods
Seafood	The dominant allergens in fish are different to those in shellfish. For a 4-6 week exclusion it is acceptable to exclude all seafood but it may only be one group (fish or shellfish) which is provoking the reactions.	• A good source of protein, omega 3 fats, calcium (fish bones), Vitamins A, D and B12, iodine • Omega 3 supplements may be required • Other nutrients can be provided by dietary manipulation	• Fish allergic individuals may tolerate shellfish and vice versa • Those with a shellfish allergy may be tolerant of other types of shellfish - an individual allergic to crustaceans (prawns, crab, lobster) may be able to eat molluscs (clams, mussels, scallops or oysters) • Professional advice is required to determine which foods are safe. • Flaxseeds / linseeds are a source of omega 3 fatty acids, as are animal products to a limited extent. • Iodine is added to iodized table salt, and seaweed, milk and eggs are other sources of iodine.
Wheat and other grains	Wheat, barley and rye are usually those grains eliminated from the diet. The following foods will therefore need to be checked: • Cakes, biscuits, pastry, desserts • Pasta, pizza • Soups, thickened sauces • Breakfast cereals • Bread, pancakes and waffles • Beer • Spelt, couscous, semolina	• Wheat products are important sources of energy, protein, fibre, B vitamins, iron, magnesium, phosphorus, selenium, zinc • B vitamin and iron supplements may be required	• Check need to avoid barley and rye • Advise alternative sources of grains e.g. oats, rice, corn, quinoa, teff and buckwheat • Check if wheat substitute foods (gluten-free products) are being eaten • Milk and eggs provide energy, protein, calcium and B vitamins • Meat can provide a good source of iron so vegetarians and vegans may require iron supplementation • Those avoiding both milk and wheat may require more supplementation as their diets may lack sufficient protein and energy as well as B vitamins, calcium, iron and trace minerals

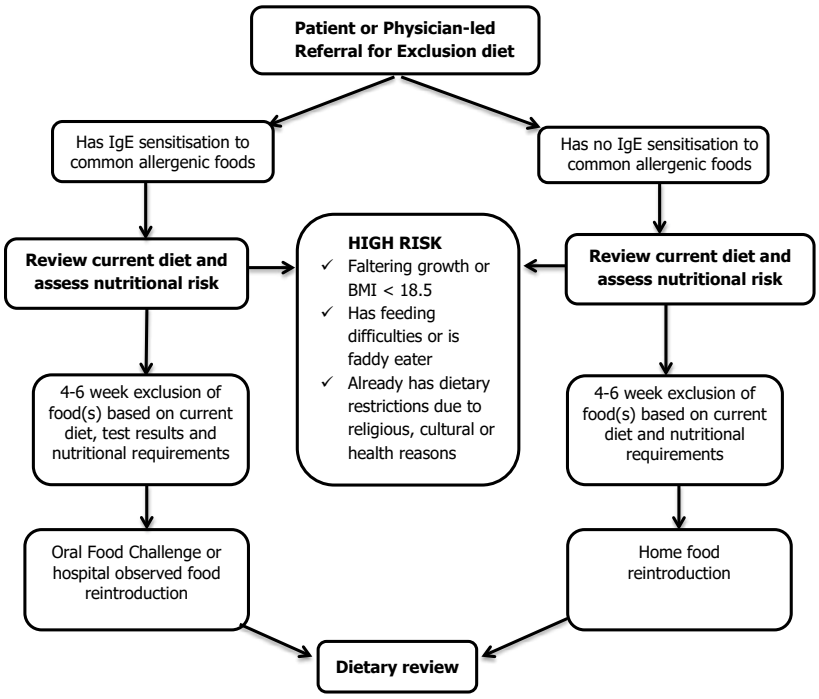

Figure 1 Algorithm for the dietary management of Atopic Dermatitis

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5 ROLE OF ALLERGY SCHOOL AND EDUCATION

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KEY MESSAGES

- A comprehensive educational multidisciplinary approach should be considered for children suffering from moderate -severe AD and their families including: healthcare professionals (dermatologist, allergist and pediatrician), a nurse trained in educational program, a dietitian and a psycologist for behavioral support
- The model and setting of the educational intervention should be framed on the local facilities including digital tools and web-based educational opportunities
- Future clinical trials should consider the cost-effectiveness of these programs and evaluate the efficacy of digital tools and web based programs

Allergic diseases are multifactorial diseases characterized by a constellation of symptoms including the skin, the nose, the lower airways and the gut often occurring at the same time in life. The patient, or the parents when a child is affected, have to deal with a chronic course with several relapses of each clinical manifestation and should be able to cope at home with most of them to reduce the burden and achieve an optimal control of the disease.

Specifically, children with atopic dermatitis (AD) are suffering by continuous pruritus, sleep disturbances and consequent behavioral disorders with profound effect on the quality of life (QoL) of the overall family. Since 2000, educational programs have been explored in AD with the aim to facilitate adherence to the treatment and ultimately improving the management and QoL with a first randomized clinical trial published in 2006.

The heterogeneity of the studies both in the format of the educational interventions and design of the research (randomized v's observational) didn't allow to draw firm conclusions in a position paper and subsequent Cochrane review. However, a multidisciplinary approach, patient-centered and family-centered, covering medical, nutritional and psychological issues has been shown to be effective in most of the intervention studies. A secondary benefit of this type of approach has been the development of a structured collaboration among the different health professionals establishing a" common language" of communication with the patient. On one hand, psychological variables (e.g. parents' abilities) at the beginning of the program appear more useful to predict the success of the educational intervention than the disease's severity according to SCORAD. On the other hand, the educational interventions have shown to be more effective in moderate to severe AD in improving QoL and reducing hospitalizations.

Another important aspect is related to the cost of such educational programs which were financially covered by various stakeholders (e.g national health system, insurances, patient's organizations and industry itself). In Germany, since 2007 a structured interdisciplinary AD education covered by national health insurances is recommended for children and families up to 7 years and children from 13 years.

More evidence should be provided also on the cost-effectiveness in future trials, which have to include self-assessment and the use of the new digital tools with web-based programs. In the meantime a comprehensive educational program should be considered for AD patients, in addition to standards of care, including medical specialists for AD treatment, a nurse for continuous guidance, a dietitian for nutritional assessment and a psychologist for behavioral support.

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6 ALLERGIC SKIN DISEASE: A GLOBAL BURDEN

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KEY MESSAGES

- Disability secondary to skin conditions is substantial worldwide, with dermatitis (atopic, contact, and seborrheic dermatitis) being the leading cause of disability due to skin diseases
- Differences exist in the magnitude of skin disease burden worldwide, particularly in the magnitude and proportion of infectious skin disease
- Despite variability in the genetic and environmental factors influencing atopic dermatitis in disparate areas of the world, AD is a global disease which is extremely common in lower and middle income settings
- Acute and chronic urticaria affect up to 20% and 5% of the general population, respectively, and these conditions can have a significant impact on patient quality of life and economic functioning
- Many treatments for allergic skin diseases have limited availability across the world, according to region and socio-economic factors

Disability secondary to skin conditions is substantial worldwide (Figure 1). Skin conditions contribute to 1.79% of the global burden of disease measured in disability adjusted life years. Dermatitis (atopic, contact, and seborrheic) is the leading cause comprising 21% of skin burden and urticaria is third highest comprising 11%. Excluding mortality, skin diseases were the fourth leading cause of disability worldwide.

Differences exist in the magnitude of skin disease burden worldwide, particularly in the magnitude and proportion of infectious skin disease (Figure 2).

Atopic dermatitis (AD) is globally prevalent, occurring across all skin tones, ethnicities, and socio-economic strata (Figure 3). Self reported AD prevalence was noted to be higher in Africa and Oceania ISAAC 3 centers, with the Indian Subcontinent, Northern and Eastern Europe reporting lower prevalence. Methodological concerns regarding the translation of terminology in many languages may affect the accuracy of these estimates, however there is no doubt that AD is a global disease, extremely common in lower and middle income settings.

Genome wide association studies show that AD is not a single disorder, rather it is a phenotype with multiple endotypes with different mechanisms and genetic susceptibilities which may vary between ethnic groups. Limited evidence suggests AD may be more prevalent in self-reported Black and mixed race populations compared with Caucasians. Explanations for this include genetic differences in loss-of-function filaggrin mutations, or abundance of distinct staphylococcus aureus strain colonising skin amongst different ethnic groups. These ethnic AD prevalence differences may, in turn, be partly responsible for different patterns of food allergy emerging amongst children of distinct ethnic groups; and the variation in predictive values of allergy tests amongst particular populations. The most effective treatments for AD (emollients and topical steroids) are available worldwide, however treatments such as topical cal-

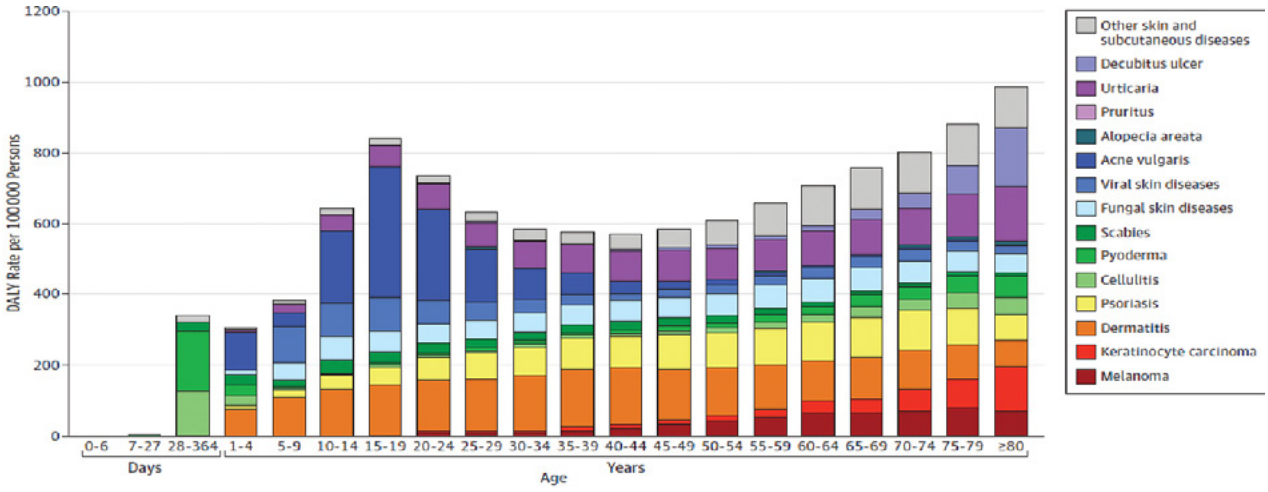

Figure 1 Disability adjusted life years (DALY) rate of skin diseases from the global burden of disease study (2013)

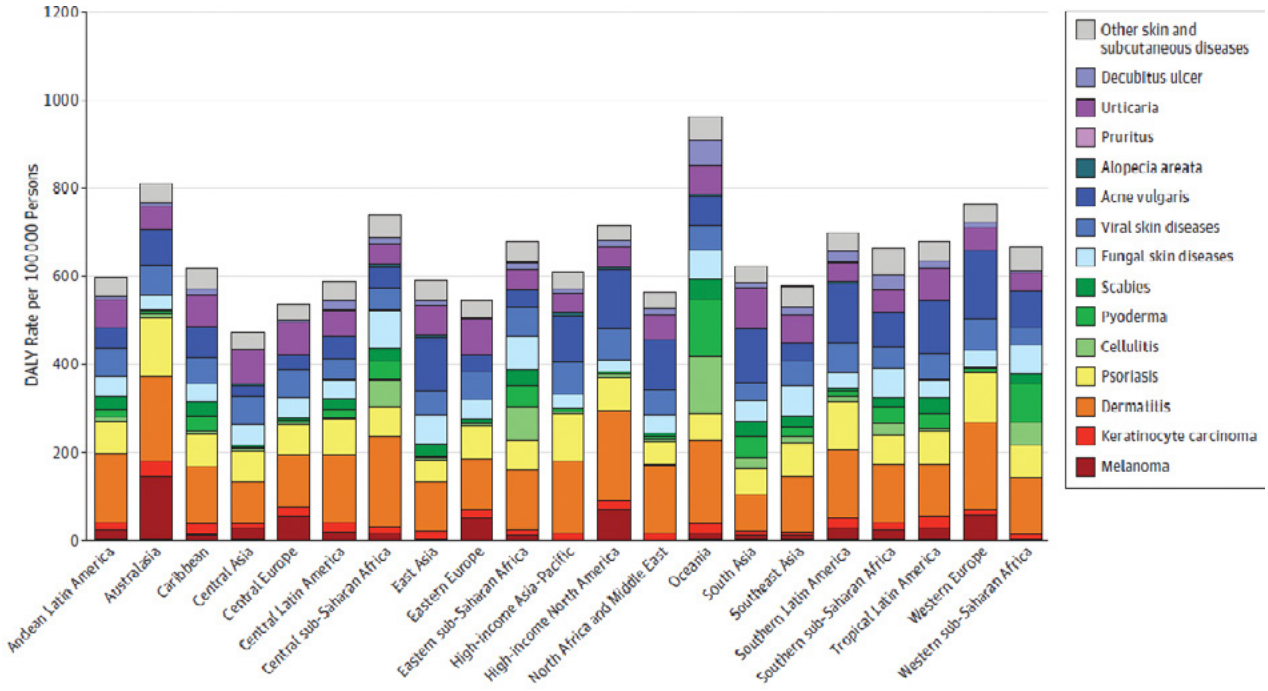

Figure 2 Regional distribution of skin disease burden from the global burden of disease study (2013)

cineurin inhibitors, phototherapy, and systemic therapies – including novel biologics - vary widely in availability according to region and socio-economic factors.

Acute and chronic urticaria affect up to 20% and 5% of the general population, respectively, and these conditions can have a significant impact on patient quality of life and economic functioning. Urticaria seems to be more uniformly distributed worldwide with less regional or ethnic variation, although data is limited from large regions such as Africa. International guidelines are mostly in agreement regarding urticaria diagnosis and management, although access to allergy diagnostics is very limited in many lower and middle income countries. Differences in the regulatory environments, availability of medications worldwide and cost restraints in the use of biologic therapies requires some flexibility and local adaptation of treatment algorithms.

Contact allergies are globally common, but because they are precip-

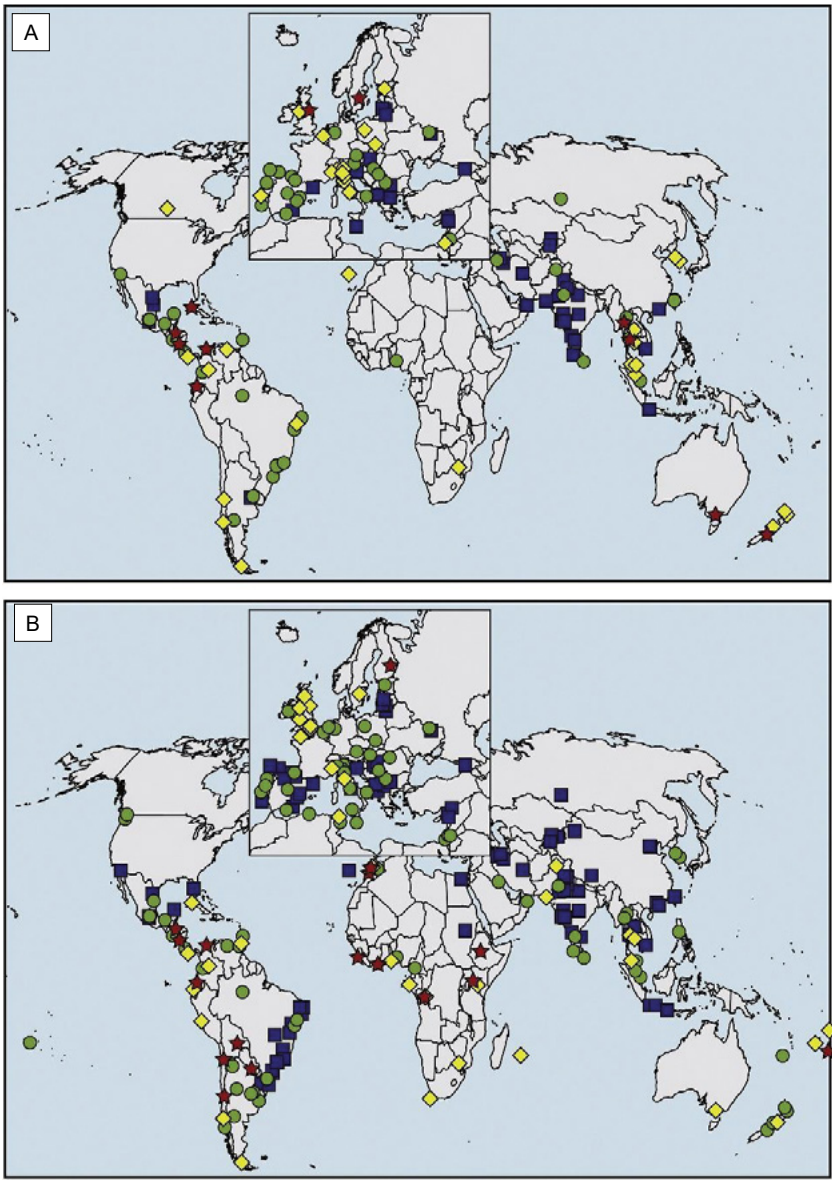

Figure 3 Worldwide prevalence of current symptoms of eczema for the age group 6 to 7 years (A) and 13 to 14 years (B). Each symbol represents a center. Blue squares indicate prevalence of less than 5%, green circles indicate prevalence of 5% to less than 10%, yellow diamonds indicate prevalence of 10% to less than 15%, and red stars indicate prevalence of 15% or more. Europe is shown in greater detail in the inset section.

itated by local allergen exposure, the prevalence and distribution of causative factors varies across the world. Furthermore, comparative data on occupational contact allergy is hindered by local differences in reporting requirements.

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Section L

IMPLEMENTATION GAP

* Generating resources for skin allergy
* Vision and roadmap to fight with skin allergy disease

1 GENERATING RESOURCES FOR SKIN ALLERGY

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KEY MESSAGES

- Allergic skin disease are an important and frequent cause of disability days in patients with allergic skin diseases
- An interdisciplinary and interprofessional approach is highly recommendable to improve care in these patients
- Health care providers, policy makers and the general audience have to be addressed to increase awareness and subsequently improv acquisition of resources dedicated for research and education and support patients with allergic skin diseases

THE BURDEN AND IMPORTANCE OF ALLERGIC SKIN DISEASES

The burden of allergic skin diseases namely atopic and contact dermatitis is very high - but due to the fact that these diseases are rarely fatal, their importance is often underestimated. However, if factors such as disability-adjusted life years (DALY) or loss in Quality of life are considered, eczema/dermatitis has the highest impact of all skin diseases in all age groups except in elderly patients where skin cancer gets more important. The economic effects have been investigated only in a few studies; the overall medical costs seem to be high and similar to those of diseases such as asthma. Atopic dermatitis is also major burden in areas with limited resources such as Sub Saharan Africa, as recently observed during an according symposium including representatives of these countries and also the WHO (www.isad.africa.org)

AN INTERDISCIPLINARY AND INTERPROFESSIONAL APPROACH IS NEEDED

Allergic skin diseases often involve other organs; e.g atopic dermatitis often associated with other atopic diseases such as asthma and /or food allergy. But also sleeping disorders and psychological problems are more commonly observed in these patients. Due to their high prevalence also primary health care providers and pediatricians are often confronted with allergic skin diseases. Thus an interdisciplinary management is crucial.

Also an approach involving several medical professions such as nurses, psychologists, nutritional specialist besides doctors has proven to be very efficient and tailored to the patients needs. In addition, patient education programs based on a multiprofessional approach were demonstrated to be highly useful and economically beneficial.

POTENTIAL RESOURCES

On one side, it is important to demonstrate the patient-related but also economic burden caused by allergic skin disease. Pharmacoeconomic studies have to reinforced that can show the primary, secondary but even more the difficult to prove tertiary costs. This will facilitate the reimbursement of such costs at least partially by health insurance systems. With the increasingly available quite costy biologicals also for allergic skin diseases, such data is even more needed. However the big financial impact of such treatments might also facilitate to generate such data. It is important to increase awareness among health care professionals, policy makers and the general public to support research, education and provide access to affordable health care for all. Also patients and their organization play an important role

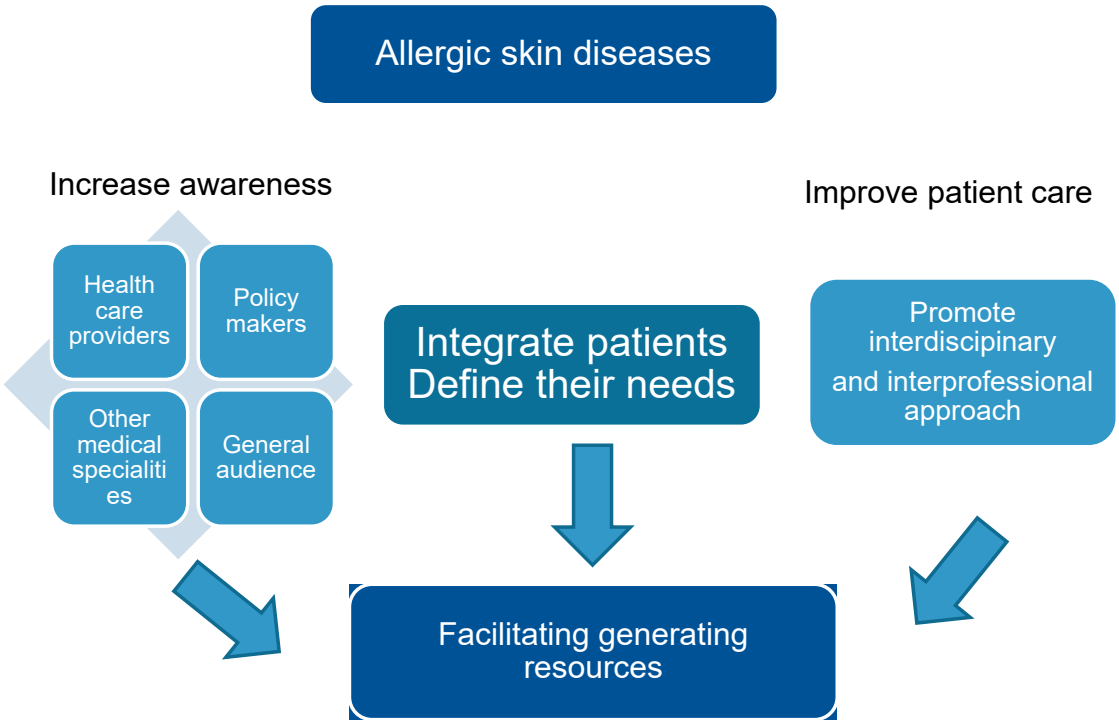

Figure 1 Generating resources for allergic skin diseases

to define their needs and to promote awareness and have to very actively integrated into this process (Figure 1).

There are few funding resources specifically dedicated to allergic skin diseases such as they exist e.g for food allergy or lung diseases. However substantial foundations such as the Bill and Melinda Gates Foundation substantially support research and education for systemic diseases to a lower extent also including skin diseases. To our knowledge, currently the Christine Kühne-Center for Allergy Research and Education CK-CARE is one of the few non-commercially-based foundations specifically dedicated to atopic dermatitis (www.ck-care.ch) with a strong focus on research and educational activities in that area. Some other grants are available by companies with a commercial background producing products for skin problems. With more products available namely for Atopic Dermatitis such grants are becoming increasingly frequent.

Indicating the psychological and socioeconomic burden and the impact of allergic skin diseases also on systemic aspects to a larger audience will facilitate the options to mobilize more resources dedicated to promote research and improve care for patients affected by these diseases.

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2 VISION AND ROADMAP TO FIGHT WITH SKIN ALLERGY DISEASE

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The term skin allergy designates cutaneous immunological hypersensitivity reactions ranging from allergic drug reactions, allergic contact dermatitis (ACD), urticaria and angioedema to atopic dermatitis (AD). Several important recent advances have been made to increase our understanding of the mechanisms and pathophysiology and novel treatment options for these diseases. Management of affected patients will likely continue to improve in the coming years as the underlying mechanisms of this disease become better understood and new therapies become available.

A worldwide strategy development: Unmet needs in the field of skin allergic diseases can arbitrarily be split into four different domains: research, development, clinical care and education. A worldwide strategy to reduce the burden of atopic dermatitis is warranted, in view of the high need to optimize patient care in the epidemic of allergic diseases. It is well established that these action plans can only be successful by the combination of efforts of all of the stakeholders: researchers, physicians, patient organizations, pharmacists, industry and policy makers. Accordingly, joining forces by all stakeholders in a unique platform that works in a network with each other is essential to reach the goal. For example, the development of new

KEY MESSAGES

- The allergy epidemic affects more than one billion patients with a global rise in prevalence, which may reach up to 4 billion affected individuals in 2050
- Atopic dermatitis is present in 10%-20% of children, with 85% of cases manifesting before 5 years of age. The prevalence of AD in adults ranges from 2% to 10%. Together with urticaria and allergic contact dermatitis the prevalence of skin allergy increases to the level of 50% of the population affected at least once in lifetime
- The already existing many unmet needs and a huge socioeconomic burden to health care systems in allergic skin diseases is expected to substantially increase
- Effective policies and strategy development are needed at the global, regional and national levels
- Efforts to overcome unmet needs should focus on 4 main directions:
  - Extensive research and development
  - Improved patient care at the global level
  - Increased public awareness and education
  - Upgrade of the allergic skin diseases and allergy in general in the political agenda
- A “Global Fight Strategy” should be developed to prevent allergic skin diseases:
  - All stakeholders should be involved
  - A multidisciplinary and scientific approach should be used
  - Next generation guidelines should be developed
  - Worldwide Skin Allergy Centers/Registries/Biobanks and integrated surveillance network should be established

TABLE 1

Global skin allergy fight strategy
• Accept allergies as a Global Public Health Problem
• Upgrade "Allergy" in the political agenda
• Appreciate the role of primary care, allied health personnel, pharmacists and dieticians as the central link between patients and physicians and initiate global education programmes
• Develop extensive health care personnel and public education and awareness programmes
• Increase research funds in general
• Prioritize prevention and curative treatments
• Develop strategies to reduce risk factors
• Strengthen the specialty of "allergology and dermatoallergology"
• Harmonize and economize the educational and awareness activities of main associations

therapies may be funneled by the identification of unmet needs and therapeutic gaps identified by patients and patient organisations, by a better understanding of disease mechanisms to be targeted identified by researchers, the development of new therapeutics addressing these mechanisms by the industry, clinical studies on efficacy and safety in patients recruited and cared for by physicians, translation of these advances into our health system by agencies and policy makers and distribution by pharmacists. On the level of patient care, modern global guidelines should be developed and implemented, particularly for the management of AD and co-morbidities. The new generation guidelines should provide structured, multidisciplinary, region and environment-oriented and individual patient-focused solutions with full considerations on differences across cultures. A global skin allergy diseases fight strategy is given in Table 1.

The **development** of novel tools for evaluation of subjective burden of the disease by the patients are needed, like user-friendly apps for the measurement of activity of skin lesions, sleep disorder, itch. **Research and development** should be synergized and prioritized in order to achieve sustainable results on epidemiology, prevention, biomarkers, novel drug development and curative treatment. There are a number of barriers and obstacles in grant giving bodies to be solved, particularly to support human immunology and allergy research (Table 2).

Treatment: The current health economic analyses in AD and urticaria neither allow comparison of treatment modalities with each other nor provide valuable data for worldwide usage. Additionally, the economical burden of AD, urticaria and ACD treatment modalities should also be considered as updated guidelines are developed. This is especially true in developing countries where medications and products are either unavailable or too expensive. Insurance coverage also plays a major role in physicians' freedom to prescribe and should be a point of discussion. Recommendations for how to navigate the potential hurdles of cost, coverage, and availability that are region-specific will be useful for health care professionals treating patients with AD. The approval of crisaborole and dupilumab for the treatment of AD marks the beginning of an exciting new era, with several other novel therapies. Likewise, the efficacy of omalizumab and several biologicals in the pipeline for urticaria is promising. Currently more than 50 candidates drugs, mostly biologicals are in the pipeline mostly in phase 2 studies. Dupilumab was the first biological approved for AD, proving for the first time single cytokine receptor chain antagonism can treat AD effectively. Nevertheless, AD and urticaria have heterogeneous phenotypes and endotypes and more treatment options are needed. In addition, there are very few data comparing the performance of these drugs against each other, in allergic skin diseases, and other allergic diseases such as asthma and food allergy.

TABLE 2

Obstacles in skin allergy diseases research
• Lack of political awareness related to low understanding and priority setting for the allergy epidemics
• Grant giving bodies have to increase their budgets for allergic diseases as they represent the highest childhood burden
• Human research is still receiving insufficient funding in many grant giving bodies as compared to animal models
• Research for prevention and curative approaches has not been so far efficiently supported
• Only small quantities of research grants are being given to hypothesis-based research
• Large scale, non-hypothesis based, in dept research with next generation DNA and RNA sequencing, exposome, epigenetic analysis and biomarkers is needed
• Allergic diseases were supported in the EU FP7 programmes to some extent, unfortunately research funds for consortium research are extremely restricted in EU Horizons 2020 programmes

TABLE 3

Major Prevention Targets linked to Mechanisms of AD
• Early diagnosis and treatment of impaired skin barrier function
• Early intervention to prevent skin barrier defect
• Prevention and treatment of type 2–skewed immune responses
• Prevention and treatment of skin microbiota dysbiosis and S. aureus overgrowth
• Prevention and treatment of epithelial dysregulation in other allergic diseases including asthma, food allergy, eosinophilic esophagitis and allergic rhinitis and chronic rhinosinusitis

Prevention: ACD is one of the most common occupational diseases and prevention is the hallmark of therapy. The exposure to contact allergens should be reduced and primary and secondary preventive measures should be implemented including educational programs. Since 85% of the AD cases occur in childhood, prevention should be taken to a very high position in the political agenda and grant giving bodies. Current data is largely inconclusive, and work in progress should be upgraded and further investigations are needed to better understand the pathogenesis to determine the most effective prevention strategies (Table 3). The concepts of prevention in urticaria are at the very early stages.

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