

POSITION STATEMENT

The role of the dermatologist in the immune-mediated/allergic diseases – position statement of the EADV task force on contact dermatitis, EADV task force on occupational skin diseases, UEMS-EBDV subcommission allergology and European Dermatology Forum

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Abstract

Background The members of the Task Force on Contact Dermatitis and the Task Force on Occupational Dermatoses of the European Academy of Dermatology and Venereology (EADV), of the European Dermatology Forum (EDF), and the members of the UEMS Section of Dermatology-Venereology (UEMS-EBDV) we want to vindicate the fundamental role that the specialist in Dermatology has in the diagnosis and management of Immuno-mediated /allergic Diseases.

Objective In disagreement with the blueprint paper of the UEMS section of Allergology (2013), in which dermatologists are excluded from one of their core activities it was decided to write this consensus paper.

Discussion The skin occupies a crucial place in the broad spectrum of allergic diseases; there is no other organ with such a multitude of different clinical conditions mediated by so many pathogenetic immune mechanisms. Subsequently, dermatologists play a fundamental role in the management of immune-mediated diseases including among others contact dermatitis, atopic dermatitis, urticaria and angioedema or cutaneous adverse drug, food and arthropod reactions. The essential role of dermatology in the diagnostic, therapeutic and preventive management of immune mediated /allergic diseases which is crucial for patient management is justified from both the academic and professional point of view.

Conclusion Based on the best care of the patient with cutaneous immune allergic disease a multidisciplinary approach is desirable and the dermatologist has a pivotal role in patient management. Be so good and no one will not ignore you, dermatologist. Ideally Dermatology should be governed according the following Henry Ford statement: "Arriving together is the beginning; keeping together is progress; working together is success."

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Why this paper?

The UEMS (European Union of Medical Specialists), a non-governmental organization representing national associations of medical specialists at European level, have defined Dermato-Venereology as the organ specialty that is responsible for the diagnosis, treatment (both medical and surgical) and prevention of diseases of the skin, subcutaneous tissue, adjacent mucosae, cutaneous appendages as well as skin manifestations of systemic diseases and systemic manifestations of skin diseases, and, of sexually transmissible diseases. Among these, allergology covers a considerable range, from contact dermatitis (irritative, toxic, allergic, photoallergic), environmental and occupational diseases to atopic dermatitis; from urticaria to all forms of acquired and hereditary angio-oedema; and from type I reactions to a wide array of skin eruptions caused by medications, food and arthropods.

Allergic diseases are continuously increasing not only in the Western World; it has been estimated that up to about 50% of the European population has a tendency to develop allergic reactions and that more than 30% may have had an allergic reaction at some time in their life. In developed countries, allergic reactions represent one of the most widespread and fast-growing chronic human health issues especially among people over 15 years of age. However, as populations get older worldwide, allergic manifestations in aged persons will occur more often in the future.^{1,2}

In a position paper, de Monchy *et al.*³ have defined dermatologists as organ-based specialists, for their expertise in a single organ, the skin. As a consequence, the text has served to potentially exclude dermatologists from one of their fundamental professional activities in the management of immune-mediated allergic and pseudoallergic diseases. Dermatologists are the experts in skin structure, biochemical and immunological functions and since cutaneous responses in allergic diseases are disease-specific,⁴ their relevant knowledge of this organ gives major advantages in differential diagnoses and therapy. Moreover, contrary to what was reported by de Monchy *et al.*,³ during their training, dermatologists in all European (and world) countries are educated in a systematic approach to skin diseases and, in particular, immune-mediated allergic diseases. For that reason, skin specialists are well known to be pivotal clinical decision-makers in these conditions, and, for their ability to coordinate other specialist care that patients with these conditions need.

The training programme in dermato-venereology includes research, clinical and laboratory activities with the possibility to access other relevant specialties in order to provide appropriate

interdisciplinary interactions.⁵ Interdisciplinary communication is a core part of a modern doctor's professional life, and it is required in many cases for optimal diagnosis and treatment.

In 12 European countries, allergology is a primary specialty, but in six European states, it is an additional part of specialist training, such as dermatology, respiratory medicine and paediatrics.⁶ In some countries, also Immunology and Clinical Immunology are recognized as independent specialty. In a recent position paper of Gerth van Wijk *et al.*,⁷ the importance has been highlighted that subspecialization exists within these medical and surgical disciplines so that allergology is practiced to the highest standards. Indeed, in those countries physicians, such as dermatologists, receive specific training in allergy in order to cover this gap. It is clearly reported that clinical diagnosis, differential diagnosis, management of diagnostic tools (epicutaneous patch tests, photo-patch tests, prick and intradermal tests, oral provocation tests or other laboratory tests as well as skin biopsies), treatment (including immunotherapies and biological therapies) and prevention of allergic, pseudoallergic and environmental diseases represent fundamental activities of the core training of dermatologists.⁷ The essential competences for optimal care are thoroughly defined in the CanMEDS framework (the most widely accepted and applied physician competency framework in the world), and it has been established that in those countries, where no full specialty in allergology exists, dermatologists are the only clinicians to have theoretical as well as practical competencies to perform patch tests and photo-patch tests.⁷ Dermatologists who specialize in allergology routinely undertake prick-, scratch- or i.c testing and undertake hyposensitization (SCIT and SLIT), and rush hyposensitization for bee and wasp venom allergies. Requesting and interpreting laboratory results are also a part of standard practice. For these reasons and with an emphasis on type IV reactions, the members of the Task Force on Contact Dermatitis and the Task Force on Occupational Dermatoses of the European Academy of Dermatology and Venereology (EADV), of the European Dermatology Forum (EDF), and the members of the UEMS Section of Dermatology-Venereology (UEMS-EBDV) are in disagreement with the blueprint paper of the UEMS section of Allergology, in which dermatologists are excluded from one of their core activities. In the discussion of virtually all socio-politically relevant topics linked to contact dermatitis and related disorders, dermatologists, and not other specialty groups, are recognized as the relevant experts by governmental and UN organizations, such as the WHO (World Health Organization) and the European Parliament. The skin occupies a crucial place in the broad spectrum of allergic

diseases; there is no other organ with such a multitude of different clinical conditions mediated by so many pathogenic immune mechanisms. Subsequently, dermatologists play a fundamental role in the management of immune-mediated diseases.

Dermatologists and immune-mediated allergic cutaneous diseases

The term 'immune-mediated allergic' cutaneous diseases include contact allergy (allergic contact dermatitis, a delayed-type hypersensitivity), contact urticaria (protein contact dermatitis, immediate-type hypersensitivity), atopic dermatitis, chronic urticaria and cutaneous adverse drug reactions. Speciality training in dermatology provides core skills to develop the specific competencies to diagnose as well as to fully consider the multiple differential diagnoses of a patient with a probable cutaneous allergic reaction.⁸ An indicative duration training of 12 months in allergic skin disease with 250–300 patients being seen during this period to achieve sufficient competence has been suggested.^{8,9} Moreover, dermatology units that specialize in immune-mediated allergic diseases are equipped with the essential tools to better investigate different disorders as well as complex cases. These departments also have access to the full range of available therapies. Particular treatments, such as biologic agents or tolerance induction protocols, necessitate a specific infrastructure. Management of immune-mediated allergic cutaneous diseases necessitates a multiprofessional team that interacts regularly to ensure that the service offered is timely, safe and effective. It is important that data should be recorded and benchmarked annually against national pooled data. Ongoing training is essential for all team members to ensure the implementation of practice that achieves quality outcomes. The number of potentially immune-mediated allergic diagnoses is high, and each of which can present in different ways with a significant impact on patients' quality of life. Although the history may be significant and a laboratory test might be crucial, the recognition and the correct description of a lesion's cutaneous morphology remains the primary key for making the diagnosis. The skin is a unique organ with its own specific immunological functions, and the multifaceted aspect of immune-mediated allergic cutaneous diseases represents one of the reasons why skin care is best undertaken by dermatologists. The major skills of dermatologists and their fundamental role in the 'allergy world' will be discussed in more detail below.

Contact dermatitis

Dermatologists have the competence to suspect and diagnose allergic contact dermatitis and assess its relevance and occupational impact. They are trained on the best practice in diagnostic patch testing in order to identify the causative contact allergen (s). With this *in vivo* test, the elicitation phase of the reaction to a contact allergen will be reproduced. Patch testing is recommended in all patients with a suspected contact dermatitis, acute

or chronic, with or without occupational relevance. This diagnostic test identifies the nature of an eczematous reaction from a wide range of possible differential diagnoses, such as genodermatoses, atopic eczema, nummular eczema, seborrhoeic dermatitis, psoriasis (mainly of the hand) and certain drug eruptions (erythema multiforme-like, lichen planus-like, granulomatous or lymphomatoid reactions).^{10–12} According to the patch test guideline made by dermatologist consensus, the severity of the reactions is scored based to its morphology.¹³ A high interobserver variability in the discrimination between doubtful and irritant reactions has been reported as well as in the distinction between doubtful and weak positive reactions.¹⁴ This underlines the necessity of continuous standardization and training in the reading and interpretation of results.¹⁴ Doubtful patch test reactions should be clarified using open tests and repeated open application tests (ROAT), particularly for cosmetics and topical drugs. However, these tests are less standardized and should be undertaken only by clinicians experienced in patch testing to ensure correct interpretation of results and minimize any risk. The next step is to determine whether that positive patch test reaction is clinically relevant or not. Dermatology training provides the competence to assess whether a recognized contact sensitization is of present, past or unknown relevance. There are many reasons for not having detected the relevance, mainly linked to clinician experience: e.g. lack of knowledge, failure to trace all sources of the allergen, inability of the clinician to elicit relevant information from the history.¹¹ The assessment of relevance is a difficult process with many potential pitfalls, and for this reason, a depth of knowledge and relevant clinical experience is required.

Atopic dermatitis

Atopic dermatitis (AD) is a chronic, inflammatory skin disease commonly managed by dermatologists, allergologists, paediatricians and some family practitioners. If different specialists treat AD with varying strategies, different outcomes may be obtained.¹⁵ Recently, a review paper compared some AD guidelines.¹⁶ The AD guideline published by the American Academy of Dermatology (AAD) 2014 working group with those created by the 2012 Joint Task Force (JTF) on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology showed notable differences. For example, about the environmental factors to avoid, e.g. sports as well as irritant sunscreen, clothing, minimizing exposure to aeroallergens without testing, elimination diet with the use of food-specific IgE antibody testing or food challenge test if results of the IgE testing are negative, the JTF support its avoidance whilst the AAD conclude that there is not enough evidence to recommend them.¹⁶ Also, a different approach concerns 'atopy patch test' as a predictive diagnostic tool for late-phase clinical reactions to proteins. Because its accuracy remains controversial,¹⁷ the Dermatologist do not recommended 'atopy patch test'^{16,18} pointing that even

classical 'patch test' in AD patients should be carefully assessed.^{13,19} The reason is the difficulty to establish the clinical relevance, owing to the generally hyper-reactive skin in AD with a higher risk of false-positive responses. These differences in the two above-mentioned papers reflect the training received by dermatologists and allergologists and also could be explained by a bias in the patient phenotype controlled: allergologists manage more extrinsic or IgE AD commonly associated with asthma and rhinoconjunctivitis, than dermatologists. Dermatologist knows that not every atopic dermatitis is IgE-associated. There is a 20% of intrinsic AD with normal total IgE values and the absence of specific IgE. This type of AD is more prevalent in female than male and in children than adult.²⁰ Nevertheless, it is important to remark that actually all these aspects got globally a consensus in the most updated European guideline, supported by Dermatologist and Allergologist published in 2018.²¹

Moreover, another phenotype of AD has recently been recognized, the adult-onset form that is rarely associated with a history of atopy.²² Dermatologists have a greater experience of these AD forms and whilst recognizing that allergy may be a trigger are more accepting of a constitutional cause compared to allergologists. More than other forms, it may be very difficult to differentiate adult-onset AD from allergic contact dermatitis, psoriasis or cutaneous T-cell lymphoma (CTCL). In particular, distinguishing early Sezary syndrome from severe AD as is the most difficult differential diagnosis, sharing not only clinical appearance but also the hallmark immunological characteristics, such as increased Th2 cytokine levels and impaired cellular immunity.²³ A good knowledge of both conditions to distinguish one from the other or at least to suspect it is required. Only a correct and careful dermatological examination together with a complete history will help the specialist reach the correct diagnosis.

Chronic urticaria and angio-oedema

Urticaria is a disease characterized by the development of weals, angio-oedema or both, involving skin, adjacent adipose tissue and mucosal tissues.^{24,25} Although diverse specialists manage it, its skin and mucosal involvement makes the dermatologist have a leading role. The differential diagnoses of angio-oedema with particular emphasis to the hereditary forms are challenging particularly during residents training in the emergency unit of the dermatology department or in the emergency department of the hospital. The same holds true for wasp and bee venom angio-oedema. Dermatology training and clinical experience enable a complete and well-structured diagnostic and therapeutic plan to be developed. The first step is to diagnose urticaria and recognize the subtypes, differentiating it from other conditions, such as urticarial vasculitis or autoinflammatory syndromes.²³ Dermatologists are well trained to manage urticaria both acute and chronic.²⁶ Dermatologists continuously update their competence regarding the spectrum of urticaria, including the advances

in our understanding of the pathogenesis, the development of new clinical tools and therapeutic approach.

Urticaria is usually diagnosed in outpatient dermatology clinics, on the basis of a structured interview, physical examination (distinct clinical morphology) and medical history.²⁵ Validated instruments for evaluating the disease activity, to induce the disease as well as assessing the impact on quality of life, are at the disposal of the trained dermatologist.^{20,27,28} Recently published guidelines give therapeutic recommendations combining dermatologists' experience and the dermatology literature.²³

Cutaneous adverse drug reactions

Skin manifestations are the commonest presentation of drug reactions.²⁹ They may range from mild to severe or life-threatening reactions.³⁰ An emergency unit or intensive care unit of every hospital more or less needs a dermatologist every day for consultation regarding differential diagnosis and management. Skin manifestations are usually the first signs of before systemic involvement. Their evaluation is critical and can provide the earliest and very important information on the severity and prognosis of an adverse drug reaction. In severe reactions, such as erythema multiforme, Stevens Johnson syndrome and toxic epidermal necrolysis, it is crucial to make a diagnosis since there is likely to be a much-improved prognosis if therapy is rapidly started. On-site biopsy with rapid processing and a dermatopathology result within 24 h is essential, for example, to differentiate staphylococcal skin scalded syndrome from drug reaction (toxic epidermal necrolysis) or from DRESS and other differential diagnoses. The spectrum of cutaneous presentations is very wide, and for this, a sound dermatological expertise is required.³¹ Another important aspect regards the situation where it may not be completely clear if the drug is really responsible especially when it is indispensable for the patient (e.g. anti-convulsants for epilepsy) and must be re-introduced if possible. In these cases, physicians must have adequate skills to perform testing procedures. A precise clinical classification of symptoms, including the morphology and time course of the reaction, is essential in order to plan a valid diagnostic work-up. Recently, experts of diverse specializations, including dermatologists, have developed guidelines addressed to all physicians involved in the management of patients with drug hypersensitivity reactions.³² The results of the overall clinical assessment, including *in vitro* and *in vivo* tests, should be discussed with the patient and documented in an 'allergy passport' that provides information on the reaction type, responsible substances, performed tests and alternative substances tested. It is important to clarify that future tolerance of the latter cannot be guaranteed with 100% certainty.³² Different from type 1 hypersensitivity, some cutaneous reaction patterns appear to have overlapping clinical features, such as T-cell-mediated-type 4 hypersensitivities, confusing physicians.³³ The most frequent cutaneous reaction patterns are type 4 hypersensitivity, which manifests as drug-induced exanthema (51.2%

vs. 12.2% as urticaria).³⁴ Drug-induced exanthema is a group of rashes some of which can resemble urticarial wheals and, thus, only a dermatologist can differentiate. Early deep dermal nodular vasculitis and panniculitis may mimic urticaria profunda, and urgent dermatopathology opinion is essential. Taken together, it is clear that making the diagnosis of a drug-induced reaction requires knowledge of the several clinical patterns and adequate, namely dermatological, skills to identify the culprit drug.

Dermatology's impact in the immune-mediated allergic cutaneous diseases

To analyse the contribution of dermatological research in the field of immune-mediated allergic cutaneous diseases, a retrospective analysis of papers published in journals regarding allergic contact dermatitis, atopic dermatitis and urticaria has been performed. The literature search was undertaken via the database PubMed. It used the following terms: allergic contact dermatitis, atopic dermatitis and urticaria. Study period was between 1 January 2017 and 30 November 2017. This analysis showed that in the study period the majority of papers on these topics were published in dermatological journals. In detail, regarding allergic contact dermatitis, 64% of papers have been published in dermatological journals, whereas only 7% in immunological and 29% in journals neither dermatological nor immunological. Similarly, for AD, 40% of papers were published in dermatological journals, 22% in immunological journals and 38% in others. Regarding urticaria, differences were smaller with a slightly higher percentage for dermatological journals (38% dermatological vs. 33% immunological journals). These data indicate that the world of immune-mediated allergic diseases is strongly connected to dermatologists' clinical practice as well as research activity.

Conclusions

Immune-mediated diseases belong to an interdisciplinary area of autoimmune and inflammatory diseases in which the dermatologist plays an important role. They represent more than 40% of diagnoses in medicine and include a substantial portion of immune-mediated allergic diseases. The latter are in continuous evolution, and the demand for specific clinical competencies is growing. In this scenario, the role of dermatologists is pivotal. Maximum efforts are undertaken for the cultivation of adequate skills and high standards of clinical patient management. The role of dermatology in immune-mediated allergic diseases within the spectrum of interdisciplinary patient management has not been addressed appropriately in the publication of de Monchy *et al.*³ The blueprint paper represents a view of management of allergic diseases, which does not currently exist and may produce harm to our patients. Allergy develops educational programs but its specific should never be isolated from dermato-venereology and other essential medical fields.^{35,36}

Interdisciplinary patient management is essential, and multidisciplinary teams for patient management are desirable. According to the 5th edition of the European Dermatology Forum White Book, skin problems outlined above require significant dermatological knowledge to be properly managed. From the scientific and economic perspective, dermatology generates value in health care for all skin diseases, including immunoallergic ones, increasing innovations with explicit patient benefits which justifies its existence, development and defence. In conclusion, we have outlined the essential role of dermatology in the diagnostic, therapeutic and preventive management of cutaneous immunoallergic diseases. Based on the best care of the patient with cutaneous immune allergic disease, a multidisciplinary approach is needed and the dermatologist has a pivotal role in patient management.

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