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A concept for integrated care pathways for atopic dermatitis —A GA²LEN ADCARE initiative

Torsten Zuberbier^{1,2}  | Amir Abdul Latiff³ | Xenofon Aggelidis⁴  |
 Matthias Augustin^{5,6} | Radu-Gheorghe Balan⁷ | Christine Bangert⁸ | Lisa Beck⁹ |
 Thomas Bieber^{10,11} | Jonathan A. Bernstein¹² | Marta Bertolin Colilla¹³ |
 Alejandro Berardi¹⁴ | Anna Bedbrook¹⁵ | Carsten Bindslev-Jensen¹⁶  |
 Jean Bousquet¹⁷  | Marjolein de Bruin-Weller¹⁸ | Dayanne Bruscky¹⁹ |
 Betul Buyuktiryaki²⁰  | Giorgio Walter Canonica²¹ | Carla Castro²² |
 Natia Chanturidze²³ | Herberto Jose Chong-Neto¹⁷ | Chia-Yu Chu²⁴ |
 Leena Chularojanamontri²⁵ | Michael Cork²⁶ | Roberta F. J. Criado^{27,28}  |
 Laia Curto Barredo²⁹ | Adnan Custovic³⁰ | Ulf Darsow³¹ | Arben Emurlai³² |
 Ana de Pablo³³ | Stefano Del Giacco³⁴ | Giampiero Girolomoni³⁵ |
 Tanja Deleva Jovanova³⁶ | Mette Deleuran³⁷ | Nikolaos Douladiris⁴ |
 Bruno Duarte³⁸ | Ruta Dubakiene³⁹ | Esben Eller¹⁶ | Batya Engel-Yeger⁴⁰ |
 Luis Felipe Ensina⁴¹ | Nelson Rosario Filho¹⁷ | Carsten Flohr⁴² | Daria Fomina⁴³ |
 Wojciech Francuzik⁴⁴ | Maria Laura Galimberti⁴⁵ | Ana M. Giménez-Arnau⁴⁶  |
 Kiran Godse⁴⁷ | Charlotte Gotthard Mortz¹⁶ | Maia Gotua²³ | Michihiro Hide⁴⁸ |
 Wolfram Hoetzenecker⁴⁹ | Nicolas Hunzelmann⁵⁰ | Alan Irvine⁵¹ | Carolyn Jack⁵² |
 Ioanna Kanavarou⁴ | Norito Katoh⁵³ | Tamar Kinaciyan⁸ | Emek Kocatürk²⁰ |
 Kanokvalai Kulthanan²⁵ | Hilde Lapeere⁵⁴ | Susanne Lau⁵⁵ |
 Mariana Machado Forti Nastri⁵⁶ | Michael Makris⁴ | Eli Mansour⁵⁷  |
 Alexander Marsland⁵⁸ | Mara Morelo Rocha Felix⁵⁹ | Ana Paula Moschione Castro⁶⁰ |
 Eustachio Nettis⁶¹ | J. F. Nicolas⁶² | Audrey Nosbaum^{63,64} | Mikaela Odemyr^{65,66} |
 Niki Papapostolou⁴ | Claudio A. S. Parisi⁴⁶ | Sushil Paudel⁶⁷ | Jonny Peter^{68,69}  |
 Prakash Pokharel^{70,71} | Luis Puig⁷² | Tamara Quint⁸ | German Dario Ramon^{70,71} |
 Frederico Regateiro⁷³ | Giampaolo Ricci⁷⁴ | Cristine Rosario⁷⁵ |
 Cansin Sackesen²⁰ | Peter Schmid-Grendelmeier^{76,77} | Esther Serra-Baldrich⁶⁴ |
 Kristina Siemens⁷⁸ | Cathrine Smith⁷⁹ | Petra Staubach⁸⁰ | Katarina Stevanovic^{1,2} |
 Özlem Su-Küçük⁸¹ | Gordon Sussman⁸² | Simona Tavecchio⁸³ |
 Natasa Teovska Mitrevska⁸⁴ | Diamant Thaci⁸⁵ | Elias Toubi⁸⁶ |

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Claudia Traidl-Hoffmann⁸⁷ | Regina Treudler⁸⁸ | Zahava Vadasz⁸⁹ |
 Ingrid van Hofman⁹⁰ | Maria Teresa Ventura⁹¹ | Zhao Wang⁹² | Thomas Werfel⁹³ |
 Andreas Wollenberg^{94,95} | Ariana Yang^{96,97} | Yik Weng Yew⁹⁸ | Zuotao Zhao⁹⁹  |
 Ricardo Zwiener¹⁰⁰  | Margitta Worm^{5,6} 

Correspondence

Torsten Zuberbier, Institute of Allergology,
 Charité – Universitätsmedizin Berlin,
 Charitéplatz 1, Berlin 10117, Germany.
 Email: torsten.zuberbier@charite.de

Abstract

Introduction: The integrated care pathways for atopic dermatitis (AD-ICPs) aim to bridge the gap between existing AD treatment evidence-based guidelines and expert opinion based on daily practice by offering a structured multidisciplinary plan for patient management of AD. ICPs have the potential to enhance guideline recommendations by combining interventions and aspects from different guidelines, integrating quality assurance, and describing co-ordination of care. Most importantly, patients can enter the ICPs at any level depending on AD severity, resources available in their country, and economic factors such as differences in insurance reimbursement systems.

Methods: The GA²LEN ADCARE network and partners as well as all stakeholders, abbreviated as the AD-ICPs working group, were involved in the discussion and preparation of the AD ICPs during a series of subgroup workshops and meetings in years 2020 and 2021, after which the document was circulated within all GAL²EN ADCARE centres.

Results: The AD-ICPs outline the diagnostic procedures, possible co-morbidities, different available treatment options including differential approaches for the paediatric population, and the role of the pharmacists and other stakeholders, as well as remaining unmet needs in the management of AD.

Conclusion: The AD-ICPs provide a multidisciplinary plan for improved diagnosis, treatment, and patient feedback in AD management, as well as addressing critical unmet needs, including improved access to care, training specialists, implementation of educational programs, assessment on the impact of climate change, and fostering a personalised treatment approach. By focusing on these key areas, the initiative aims to pave the way for a brighter future in the management of AD.

KEYWORDS

atopic dermatitis, eczema, guidance, ICP, integrated care pathways, multidisciplinary, prevention, treatment

1 | INTRODUCTION

The Global Allergy and Asthma European Network, GA²LEN, originally started in 2004 as the European Union network of excellence in collaboration with EAACI (European Academy of Allergy and Clinical Immunology), is the largest multidisciplinary network of research centres and clinical care in allergy and asthma. The ADCARE group is a sub network within GA²LEN for expertise in atopic dermatitis (AD) that collaborates in research and educational activities as well as in exchange of experience in novel and emerging approaches to treat severely affected patients.

AD is a common chronic inflammatory skin disease representing a lifelong disposition with variable clinical manifestations and expression. The prevalence rates might vary between studies depending on the geographical, genetic, and methodological differences. Cross-sectional surveys report point prevalence, ranging across countries from 2.1% to 4.9% in adults and from 2.7% to 20.1% in children.^{1,2} In The Odense Adolescents Cohort Study, AD persisted into adulthood in 50% of those diagnosed in school age.³ A nationwide Norwegian health registry suggests an increase in the incidence rate of paediatric AD, especially among children younger than 1 year. During the study period, more than 1 in 6 children younger than

6 years had, at some point, been affected by AD.⁴ This represents a significant burden of the disease, warranting effective, efficient, and broadly applicable management strategies that appreciate the complex and variable nature of AD.⁵

AD is a systemic inflammatory condition, including flaggrin deficiency-induced skin-barrier disruption and microbiome alteration. Targeting the pathogenesis of AD, a multifaceted approach, including skin hydration, measures to strengthen skin barrier integrity, topical anti-inflammatory and antipruritic therapy, antibacterial measures, and the elimination of exacerbating factors, can help achieve disease control and prevention of comorbidities. However, many factors limit consistent adherence to treatment plans, such as concerns about side effects, difficulty following time-intensive and complex skin care routines, the economic burden of therapies, and challenges with lifestyle modifications. Patients with AD have sleep problems very commonly and are also at higher risk of mental health disorders, such as attention-deficit/hyperactivity disorder, anxiety, depression, disorder of behaviour, autism, and suicide. The visible and chronic nature of AD impacts the quality of life and can contribute to psychological stress, which in turn is a known trigger of itch and skin flares, creating a challenging vicious cycle. Furthermore, bullying is an undesirable consequence of AD that impairs the quality of life.^{6–8}

A multidisciplinary concept of management and care is needed, considering atopic and non-atopic comorbidities, aiming for the detection and identification of atopic status, the elimination of exacerbating factors, a fast and effective management of exacerbations as well as long-term disease control (Figure 1A,B).^{17–21} Accordingly, approaches have been developed in appreciation of the complex interplay among biological, psychological, behavioural, and dietary factors and the wide range of knowledge, skills, and support

that patients and families require to effectively manage and cope with this condition.⁶ In consideration of the complex pathophysiology and heterogenous clinical phenotype of AD, more individualised preventative and therapeutic strategies are desirable.²²

A comprehensive consensus-based S2k-guideline for the treatment of children and adults with AD was published as a joint interdisciplinary European project, including physicians from all relevant disciplines as well as patients.²³ This guideline was upgraded to the S3 level and published in 2022.^{24,25}

While evidence-based guidelines form the basis of AD management, treatment strategies that are used in daily practice are far from guidelines and show significant variation in different jurisdictions or geographical regions. Integrated care pathways (ICP) not only consider different guidelines but can also fill the gaps by providing an expert discussion result based on clinical practice experience of real-life patient treatment journeys. ICPs offer structured multidisciplinary plans for patient management and have the potential to enhance guideline recommendations by combining interventions and aspects from different guidelines, integrating quality assurance and describing co-ordination of care.²⁶ Hence, ICPs can also consider the different contexts of lower- and middle-income countries as reflected in national guidance.²⁷

AIRWAYS ICPs are an example of a multidisciplinary approach to reduce the burden of chronic respiratory diseases, their mortality and multimorbidity, and in the long term to promote active and healthy aging (AHA).^{28,29} The non-governmental organisation Allergic Rhinitis and Its Impact on Asthma (ARIA) has promoted the integration of its recommendations in ICPs using mobile technology to reinforce self-management and the implementation of guidelines.^{30–32} Following this successful example, a similar strategy of

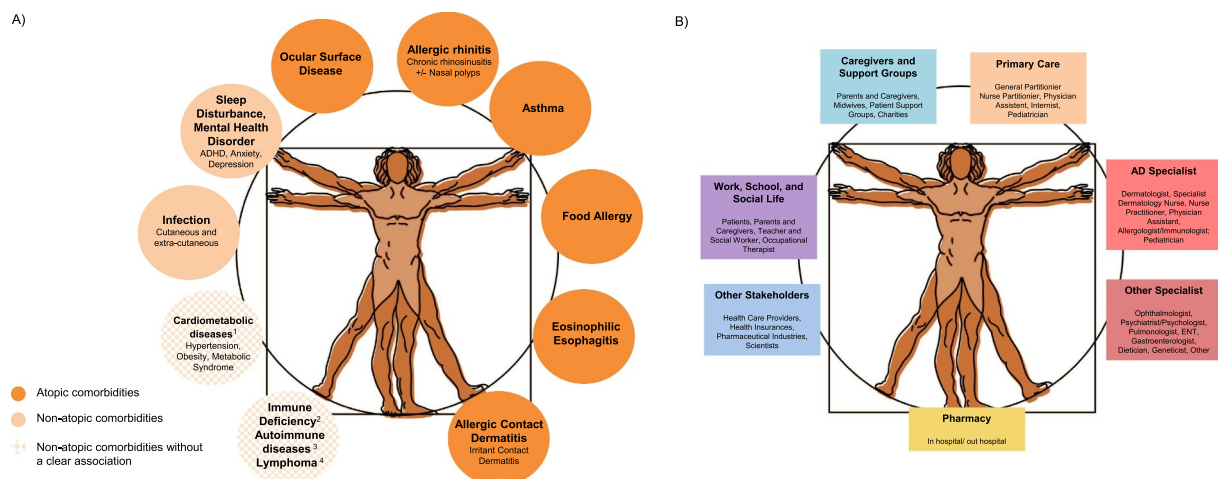


FIGURE 1 (A) More than skin diseases—comorbidities in AD.^{9–13} At present, US and Asian data indicate cardiometabolic diseases as a comorbidity of AD, while data from European patients do not support this. Lymphoma is controversially discussed—it is possible that the ‘association’ to AD is based on a misdiagnosis of early stages of CTCL.¹⁴ For example, hyper IgE syndromes, WAS and WAS-like conditions; IPEX and IPEX-like conditions, CBM-opathies (CARD11 deficiency, CARD14 deficiency, MALT1 deficiency).³ New data indicate autoimmune comorbidities in adults with AD, for example, rheumatoid arthritis, inflammatory bowel disease, and alopecia areata.^{15,16} Lymphoma is controversially discussed—it is possible that the ‘association’ to AD is based on a misdiagnosis of early stages of CTCL. (B) The AD multidisciplinary team. Please note the country-specific differences, for example, in some countries, children are usually not seen by the GP during their first years of life but by primary care pediatricians. Hence, pediatricians as well as AD specialists are included as primary care providers. AD, atopic dermatitis; CTCL, cutaneous T cell lymphoma.

digitally enforced ICPs has been proposed for the setting of AD, to translate guidelines into clinical practice and to treat AD in the context of allergic comorbidities including asthma and food allergy as well as non-allergic comorbidities such as inflammatory bowel disease and psychological disorders through the coordination between multidisciplinary teams. This publication represents the result of the GA²LEN ADCARE initiative based on three conference meetings.

2 | OBJECTIVES

The general objective of the AD-ICP working group is to provide a pragmatic and practical support to optimally manage the disease and its comorbidities globally.

AD-ICPs do not duplicate existing professional guidelines or national prevention programs but aim to strengthen them where appropriate and to help improve adherence to guideline recommendations by translating them into practice, integrating aspects from different guidelines and adjusting them to real-world conditions in a dynamic way. ICPs also contain information on how to combine therapies for AD and related diseases.

A holistic approach is strived to improve multidisciplinary communication, including primary care, to improve clinician-patient communication and patient satisfaction, to empower patients and their caregivers, and to engage them following the concept of shared decision making. Accordingly, AD-ICPs are designed to be carried out by a multidisciplinary team including the support of technology-assisted patient activation by mobile health tools to enhance self-management and adherence to guidelines and to serve as a platform for patients to share their experiences.

The detailed objectives, challenges, and unmet needs in the management of AD have been published separately.³³

3 | DEVELOPMENT OF THE AD ICPs

3.1 | Expert discussion

GA²LEN ADCARE has taken the lead, informing upfront EAACI, EADV and WAO about the initiative and asking for their involvement in the future, requesting them to send delegates. Other societies will be informed and asked for involvement at a later stage.

The core of the AD-ICP working group consists of speakers at an online conference held on 26 March 2020. Based on the results of the discussion of several specific working subgroups, the ICPs were then comprised following a structure with boxes indicating the different levels at which certain knowledge and interventions are required.

A second meeting was held on the 12 and 13 of August 2021 with dedicated workshops regarding different topics. Afterwards the document was circulated with all GAL²EN ADCARE centres.

3.2 | Stakeholders

The document involves all stake holders, including the patients, pharmacists, nurses, general practitioners and pediatricians, specialist, tertiary referral centres, the hospitals, academic research institutions, the pharmaceutical industry, and patient organisations. Additional stakeholders not involved in the preparation of the document but included as discussion partners are healthcare institutions, healthcare providers and policy makers.

The document also supports the EU efforts on healthy and active aging (AHA) with GA²LEN being a partner in the EIP initiative on AHA.

4 | ATOPIC DERMATITIS INTEGRATED CARE PATHWAYS

Due to variable clinical manifestations, the variety of available treatments, and in order to become comfortable to take over responsibility for the treatment of their chronic condition, patients and their caregivers need clear and easy-to-understand strategies for their individual needs that will allow them to assess, ask, adjust and act.⁶

Different levels of support are available to assist patients in the management of their disease. Figures 2A–H and 3 outline the ICPs for AD involving all stakeholders and self-management aspects for supporting patients with AD. Patients can enter the ICPs at any level depending on AD severity, resources available in their country, and economic factors such as differences in insurance reimbursement systems. While the AD-ICPs aim to include as many stakeholders as possible, country-specific differences need to be considered, such as the role of nurse practitioners, which does not exist in all countries. Also, in some countries, children are usually not seen by the GP during their first years of life but by primary care pediatricians.⁴¹ Also, a large proportion of all patients with AD suffer from a mild form of the disease and could be managed mainly by the GP, primary care pediatrician and nurse practitioners. Pharmacists are a further, valuable source of support, especially for patients with mild disease, and should therefore be more involved in AD care.

Adherence to AD therapy is often poor, particularly to adequate moisturiser application and to topical corticosteroid (TCS) treatment, the latter mainly due to the fear of side effects and steroid withdrawal symptoms.^{42,43} GPs and primary care pediatricians are in a key position to improve compliance before specialist referral and the next treatment steps to more potent therapies are considered. Patients need to be educated to build up the competence and the confidence to consequently manage acute flares and long-term maintenance treatment, which is known to effectively promote disease control.⁴⁴

Patients with AD have a high risk of atopic as well as non-atopic comorbidities (Figure 1A). For example, they have a significant and disease severity-dependent increased risk of the development of

A)



B)

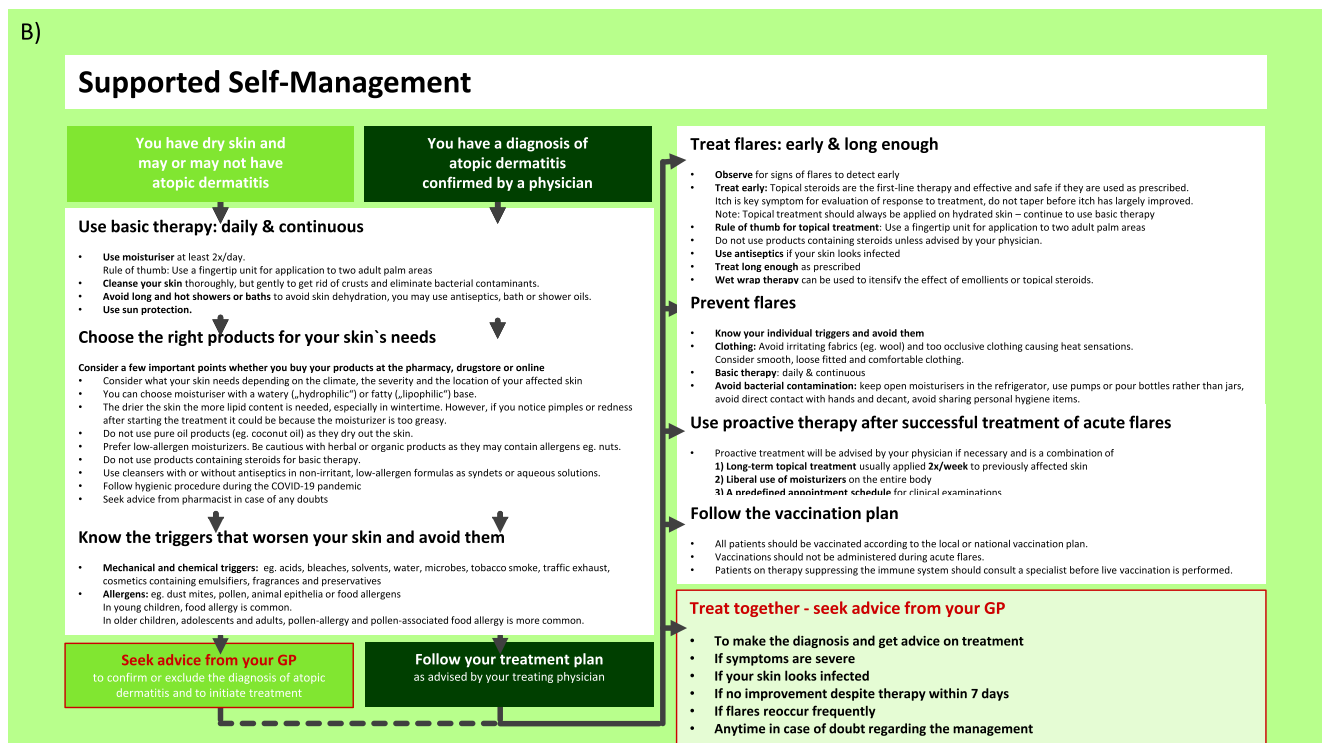


FIGURE 2 (A–H) ICPs for the management of atopic dermatitis. (A) ICP—overview. (B) Supported self-management.^{20,23} (C) Pharmacy.^{20,23,34,35} (D) Primary care.^{20,23,36,37} (E) Specialists I.^{20,23} (F) Specialists II.^{20,23} (G) Caregivers and support groups. (H) Work and social life. ICPs, integrated care pathways.

ocular morbidities, which might affect 25%–42% of AD patients. These are often underdiagnosed and underrated—even by the specialists—and can in some cases result in permanent corneal damage.^{45–47} Awareness and early referral to a dedicated specialist in case of any suspicion is paramount.

Of equal importance and often overlooked are psychosomatic and psychiatric morbidities such as sleep disturbances in time and quality, anxiety, and depression.⁴⁸ Effective screening should systematically be part of AD management and therefore has been included in the AD-ICPs.

C)

Pharmacy

Advise on basic therapy: daily & continuous

- Moisturisers** are the mainstay of AD management with a short- and long-term steroid sparing effect. They should be used liberally and frequently (min. 250 g/week for adults).
 - Recommended:**
 - >2x/day moisturisers
 - Only non-irritant preparations devoid of allergens or potentially allergenic proteins/haptens known to cause contact allergy
 - Hydrophilic or lipophilic base, higher lipid content in winter
 - Add-on: barrier ointments, bath oil, shower gel, emulsions, micellar solutions
 - Not recommended:**
 - Pure oil products, eg. coconut oil, as they dry out the skin
 - Moisturisers containing **tannin- and ammonium bituminosulphonate (ichthammol)** may be a useful addition.
 - Emollients **'plus'** contain saponins, flavonoids and riboflavins from protein-free oat plantlet extracts, or bacterial lysates. They improve AD lesions and influence the skin microbiome.
 - Beware of side effects eg. acne- or rosacea-like symptoms due to too greasy products in the face.
- Infants/Toddlers**
 - Urea may cause irritation and kidney dysfunction and should be avoided in infants. Toddlers should be treated with lower concentrations than adults.
 - Propylene glycol** is irritating in children <2 years and should not be used.
 - Allergens** such as peanut allergens or colloidal oatmeal contained in moisturisers may cause skin sensitization and allergy. Only moisturizer preparations devoid of allergens and haptens known to cause contact allergy (eg. lanolin/wool like alcohol or methylisothiazolinone) should be used, especially <2 years of age.
- A **finger tip unit (FTU)** is the amount of ointment expressed from a tube with a 5-mm-diameter nozzle, measured from the distal skin crease to the tip of the index finger (~0.5 g); adequate amount for application to two adult palm areas.
- Sun protection** with low-allergen formulas is recommended, in particular when on TCI treatment
- Skin cleansing and desinfection** is important to get rid of crusts and eliminate bacterial contaminants. Syndets or aqueous solutions with/without antiseptics in non-irritant, low-allergen formulas can be used. Adding antiseptics to the bathwater may be useful.
 - Skin care during the COVID-19 pandemic:** AD patients should observe hygienic procedures with hand wash and disinfectants using non-irritant soap substitutes in the same way as directed for soap.
- Pre- and probiotic mixtures** such as lactobacilli are currently not recommended due to lack of evidence of effect. Though emollients with bacterial lysates have been shown to improve AD lesions and skin microbiome of AD.

Avoid incorrect diagnosis and encourage treatment adherence

- Ask the patient whether the diagnosis is physician-based.
- Ask and advise about prescription medications, encourage trust and treatment adherence

Support treatment and prevention of acute flares: early & long enough

- Early treatment** is important and should be encouraged.
- Topical treatment is prescribed by GPs and specialists and should be used as recommended.
- 1st line: Topical corticosteroids (TCS)** significantly improve skin lesions.
 - Dose tapering is usually not required. To spare steroids and avoid side-effects use them intensively during acute flares.
- 2nd line: Topical calcineurin inhibitors (TCI)** significantly improve skin lesions.
 - Tacrolimus ointment and Pimecrolimus cream are licensed for AD treatment.
 - TCI are indicated also in sensitive skin areas (facial, intertriginous, anogenital).
 - Effective sun protection is recommended.
 - TCI may cause burning sensation and transiently worsen AD.
- Patient fear of side-effects** should be recognized and addressed to improve adherence and avoid undertreatment.
- Itch is key symptom for the evaluation of treatment response.**
 - Tapering should not be initiated before the itch has largely improved.
 - Topical treatment should always be applied on hydrated skin.
 - Use a **finger tip unit (FTU)** for topical treatment
 - Proactive therapy**, eg. twice-weekly application in the long-term follow-up, may help to reduce relapses.

Advise on antipruritic therapy

- Recommended:**
 - TCS in the initial phase of exacerbation; TCI until clearance of eczema
 - Topical polidocanol may be used
- Not recommended:**
 - Routine clinical use of topical antihistamines including doxepin, cannabinoid receptor agonists, opioid receptor antagonists or anesthetics
 - HR antihistamines are generally not recommended. They may be tried, if TCS and moisturizers are not sufficient. In children, long-term use may affect sleep quality and is therefore not recommended.

Treat together - refer to a GP

- If no physician-based diagnosis of atopic dermatitis
- If symptoms are severe
- In case of signs of superinfection
- If no improvement despite therapy
- If symptoms frequently relapse
- Anytime in case of any doubt regarding the management

D)

Primary Care (GP, Nurse Practitioner, Pediatrician)

Diagnose & assess severity

- Diagnostic criteria for adult and pediatric patients
- Assessment of severity:** SCORAD score or rule of thumb
 - mild** SCORAD <25: need for intermittent topical anti-inflammatory therapy; no restrictions in daily activities
 - moderate** SCORAD 25-50: need for continuous topical or proactive therapy
 - severe** SCORAD >50: need for systemic therapy; disease-related restrictions on daily activities
- Treatment goals are defined by the patient's disease burden**

Initiate and monitor basic therapy to treat dry skin (see „Pharmacy“)

- Early treatment** is important and should be encouraged.
- 1st line: Topical corticosteroids (TCS)** significantly improve skin lesions.
 - TCS potency** (Note: classification might differ in different countries)
 - EU (excl. France): TCS grouped by potency according to Nidner from mild (group I) to superpotent (group IV)
 - US: TCS potency grouped from VII (weakest) to I (strongest)
 - Mild TCS** (Nidner groups I and II) for treatment of the face and especially the eyelid region
 - Potent and very potent TCS** (Nidner groups III and IV) more likely to cause adrenal depression than group I and II, but systemic effects decrease more quickly due to more rapid restitution of the skin barrier, only prescribed by specialist
 - Superpotent TCS** (Nidner group IV) not recommended, especially not in children, only prescribed by specialist
 - Children should be treated with less potent TCS than adults.
 - Dose tapering usually not required. To spare steroids and avoid side-effects use them intensively during acute flares.
- 2nd line: Topical calcineurin inhibitors (TCI)** significantly improve skin lesions short- and long-term.
 - Tacrolimus ointment and Pimecrolimus cream are licensed for AD treatment.
 - Anti-inflammatory potency: 0.1% tacrolimus = TCS with intermediate potency > 1.0% pimecrolimus
 - Indicated also in sensitive skin areas (facial, intertriginous, anogenital); effective sun protection recommended
 - May cause burning sensation and transiently worsen AD
- Topical treatment should always be applied on hydrated skin
- Patient fear of side-effects** should be recognized and addressed to improve adherence and avoid undertreatment.
- Itch is key symptom for the evaluation of treatment response.**
 - A topical treatment break should not be initiated before the itch has largely improved.
- Systemic steroids** should not be prescribed. Refer to a specialist for advice on systemic treatment option.
- Optimize before switching substances or switching from topical to systemic treatment**
- Proactive therapy**, eg. twice-weekly application in the long-term follow-up, may help to reduce relapses
 - With mild disease activity, liberal use of moisturizers with TCS 2-3x/week (per month mean range of 15 g (infants), 30 g (children), 60-90 g (adolescents/adults), adapted to affected BSA) allows good maintenance. Such amounts of even potent TCS usually do not have adverse systemic or local effects and may be used safely for at least 20 weeks.

Educate and monitor treatment adherence

Screen for signs of superinfection and initiate treatment

- Topical antiseptics** should be considered in patients with treatment-resistant AD.
- Silver-coated, acid-coated and silk textiles and chitosan** may be used to decrease *S. aureus* colonization and itch.
- A short course of systemic antibiotics**, such as cephalexin, may be considered in patients infected with *S. aureus*.
- Topical antibiotics** are not recommended for long-term application.
- Ecema herpeticum** should be treated without delay using systemic aciclovir.
- Topical or systemic antifungal** therapy may be effective in some patients.
- Vaccinations** should be administered according to recommendations, though not during acute flares.

Identify triggers by history and basic testing

- Mechanical and chemical triggers** eg. acids, bleaches, solvents, water, microbes, air pollutants such as tobacco smoke, volatile organic compounds (VOCs), traffic exhaust, cosmetics containing emulsifiers, fragrances and preservatives
- Allergens** eg. dust mites, pollen, animal epithelia or food allergens
 - Measure total IgE and specific IgE for age- and history- adapted common allergens, refer to specialist in case of doubts
 - Note: allergen sensitization is often not coupled with clinical symptoms
 - Infants/toddlers: check food allergens if ≥ moderate AD (frequent: cow's milk, hen's egg, peanut, soya, nuts, fish, wheat)
 - Children/adolescents/adults: consider aero allergens and pollen-associated food allergy

Be aware of comorbidities

- Patients with AD have a high risk for atopic as well as non-atopic comorbidities.
- Atopic comorbidities** eg. allergic rhinitis,
- Psychiatric/psychosomatic comorbidities**
- Ocular comorbidities** eg. conjunctivitis, keratitis, keratoconus or glaucoma
 - Effective treatment of eyelid dermatitis/blepharitis is important to prevent permanent damage to the eye.
 - TCS and TCI can both be used on the eyelid: in the acute phase TCS, then TCI (no harm if ointment comes into the eye)

Treat together - refer to specialist (systemic treatment)

- If diagnosis unclear
- If moderate to severe AD
- If no improvement with well-conducted topical treatment OR need for daily treatment for several weeks OR need for high-potency steroids OR need for systemic treatment
- If basic allergy testing insufficient for diagnosis and recommendations
- If concerns about ocular comorbidity
- If concerns about psychosomatic/psychiatric comorbidity

FIGURE 2 (Continued)

4.1 | Diagnostics in AD—Should treatment targets be based on clinical scores, or on symptoms/QoL? What is feasible in a daily practice setting?

In the primary care setting, diagnosing, and staging of AD should be based on clinical criteria including the assessment of itching and sleep disturbance using visual analogue scales and overall quality of life. An adaptation of the diagnostic approach to the patients' age is required.

The recommended diagnostic tool should be simple and could be supported by digital applications.

Differential diagnosis is important and potentially challenging, as for example, early stages of cutaneous T-cell lymphoma might be misdiagnosed in patients with AD.⁴⁹

Criteria for AD specialist referral (see Figure 1B) should be provided considering the distribution pattern (localised vs. wide-spread, extent and localisation of affected body surface area), the

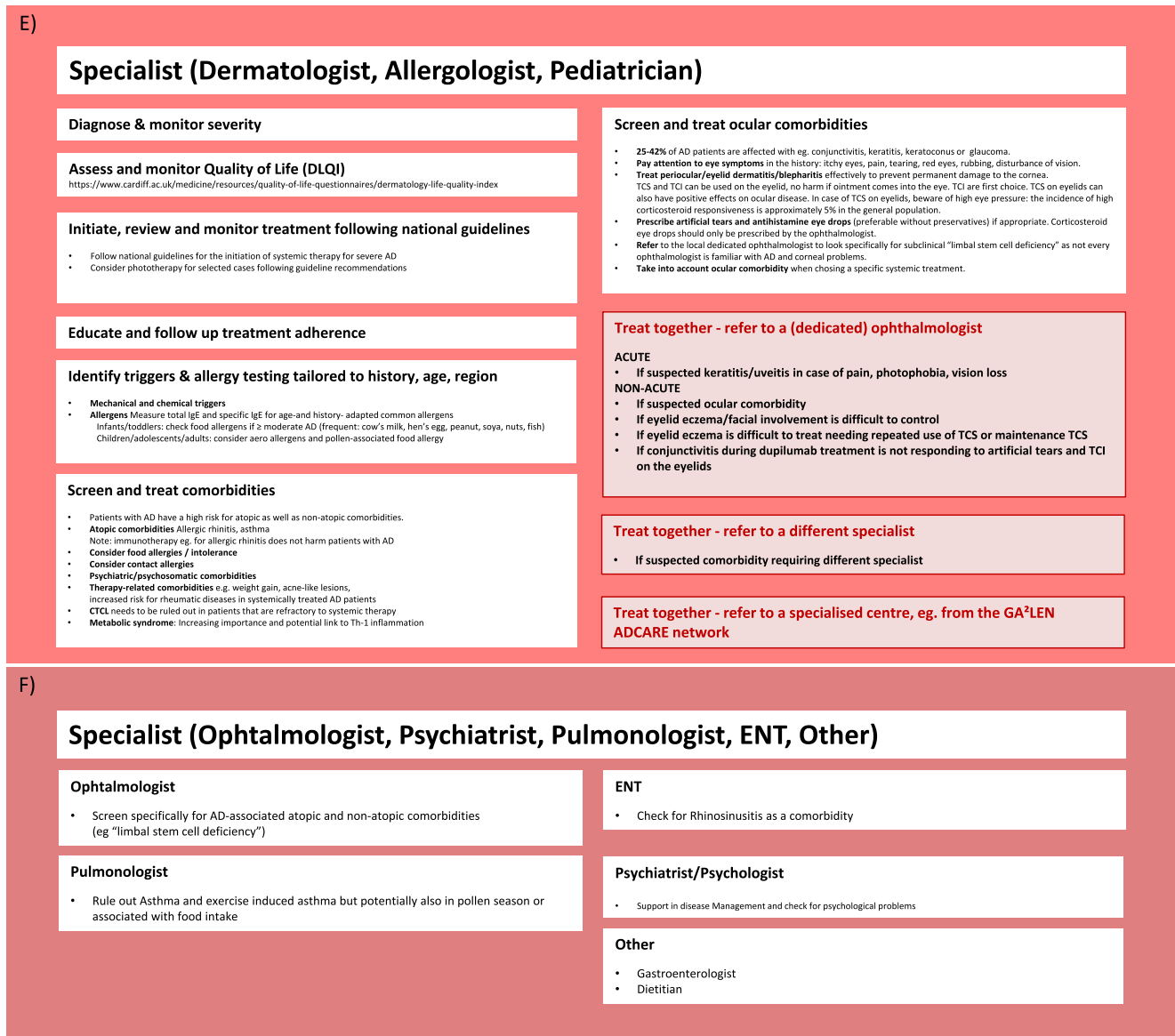


FIGURE 2 (Continued)

need for daily treatment for several weeks, the need for high potency steroids, the response to treatment, the recurrence of symptoms, infections, the presence of comorbidities, the age of disease onset, and the impact on quality of life.

Scores, such as SCORAD, EASI, POEM, or DLQI/cDLQI, should be reserved for specialists as training in using these scoring systems is crucial.

4.2 | Comorbidities in AD

Atopic and non-atopic comorbidities have a considerable impact on disease burden and treatment options and require a multidisciplinary, integrated concept for their prevention, early detection, monitoring,

and treatment (Figure 1A). Early treatment considering all comorbidities might prevent the atopic march in selected individuals.⁹⁻¹¹

For example, contact allergies in patients with AD require consideration when choosing the type of topical treatment. With regard to food allergies, it is important to distinguish between small children and adults, between immediate and delayed reactions, and between allergy and intolerance for a better description of the potential phenotype of AD that may have implications for different systemic therapies.

The knowledge on non-atopic comorbidities in AD is increasing; however, the associations are not yet fully understood. For example, new data indicate autoimmune comorbidity in adults with AD, especially autoimmune dermatological, gastrointestinal and rheumatological diseases.^{15,16} Furthermore, the potential link of the

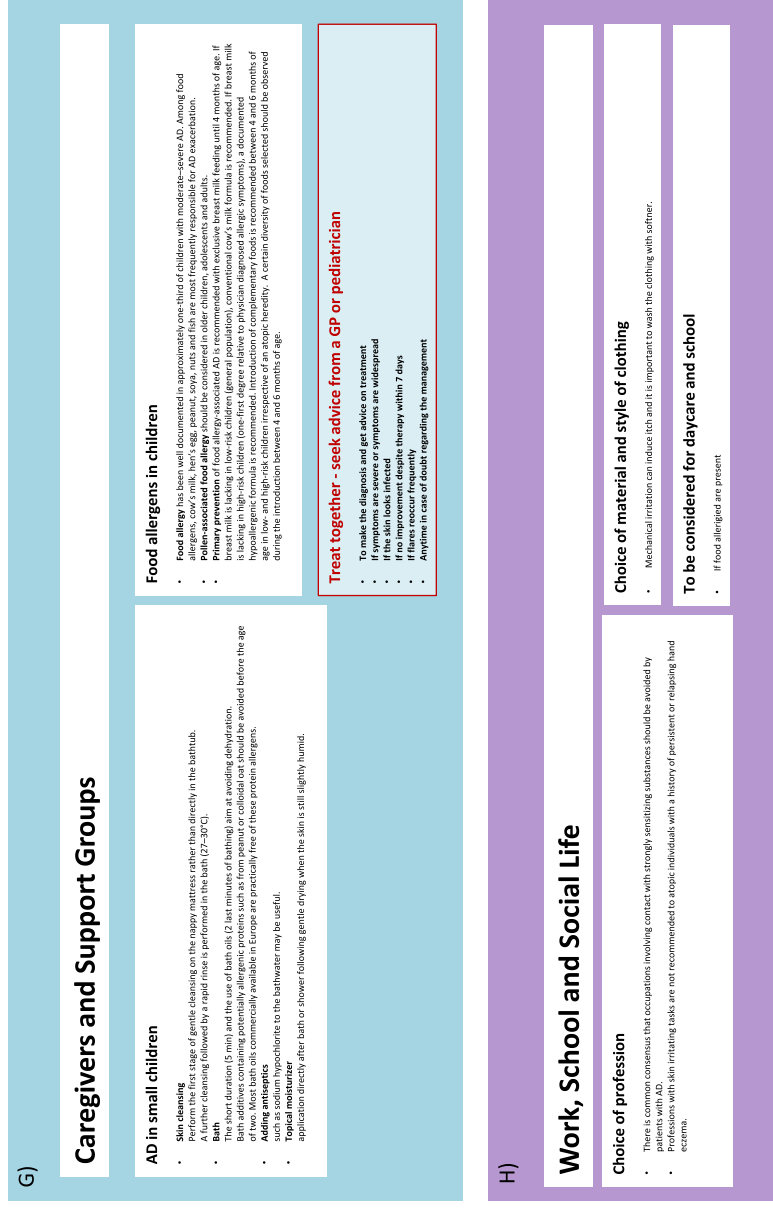


FIGURE 2 (Continued)

A)

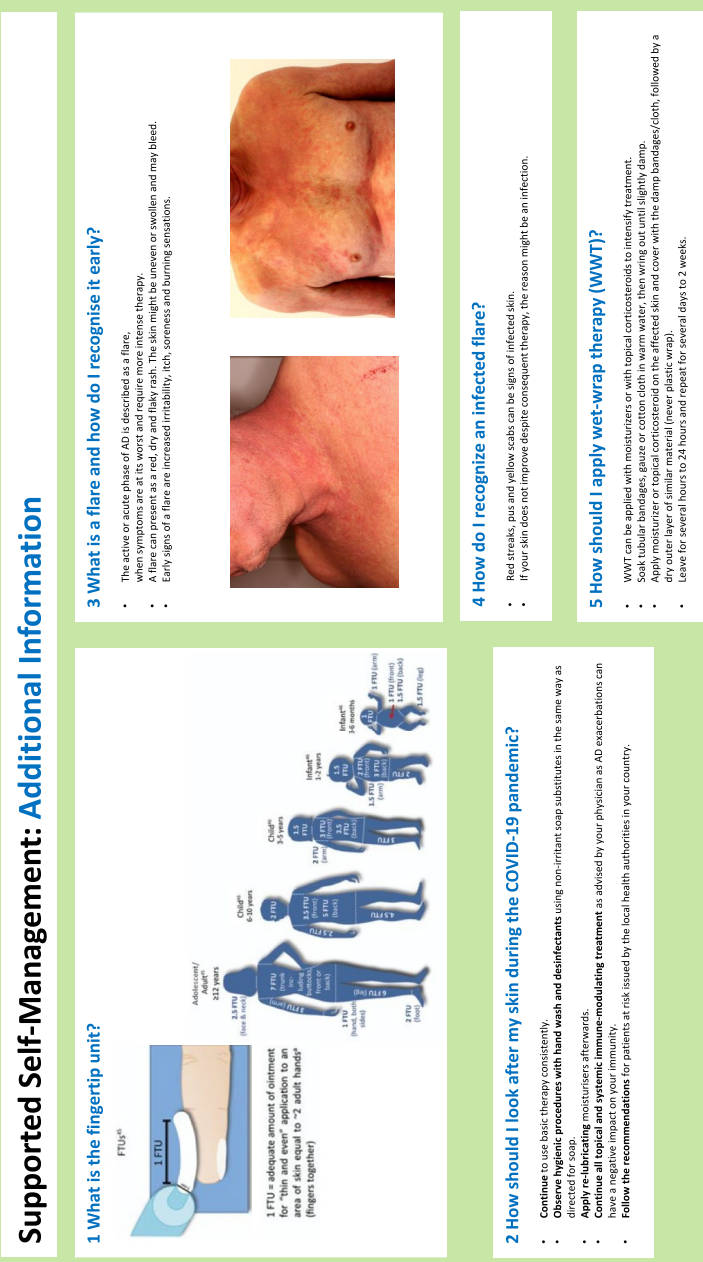


FIGURE 3 ICP—additional information. (A) Supported self-management.^{20,23,34,37,38} (B) Pharmacy.³⁸ (C) Primary care I.^{36,37} (D) Primary care II.^{20,23,39,40} (E) Specialist (dermatologist, allergologist, pediatrician).²⁰ ICPs, integrated care pathways.

B)

Pharmacy: Additional Information

1 Overview Moisturisers

- **Hydrophilic base**
Urea 5%
- **Lipophilic base**
- **Optional add-ons**
Barrier ointments
Bath oil
Emulsions
Micellar solutions
- **Antiseptics**
sodium hypochlorite
octenidin
polihexanid

2 Overview topical treatment

Class: Corticosteroids

Low-potency

- Hydrocortisone acetate 1% cream/ointment
- Desonide 0.05% cream/ointment

Mid-potency

- Betamethasone valerate 0.05% or 0.1% cream/ointment
- Mometasone furoate 0.1% Cream
- Hydrocortisone valerate 0.2% cream/ointment

High-potency

- Fluocinonide 0.05% cream/ointment/gel
- Mometasone furoate 0.1% ointment
- Desoximetasone 0.25% cream/ointment/gel

Very high-potency

- Betamethasone dipropionate glycol 0.05% ointment
- Clobetasol propionate 0.05% cream/ointment
- Halobetasol propionate 0.05% cream/ointment

Class: Calcineurin inhibitors

- Tacrolimus 0.03% ointment
- Tacrolimus 0.1% ointment
- Pimecrolimus 1% cream

3 Questions to ask the patient with AD to identify the need for GP referral

- Does AD prevent you from participating in social activities
- Does AD prevent you from sleeping well
- Does AD have an impact on your school or work life.

Any of the 3 questions are answered with yes. Patients should be recommended to see their physician.

C)

Primary Care I: Additional Information

1 Diagnostic criteria for adult and pediatric patients

Must have 3 or more basic features:

- Pruritus
- Typical morphology and distribution:
Flexural lichenification or linearity in adults
Facial and extensor involvement in infants and children
- Chronic or chronically-relapsing dermatitis
- Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

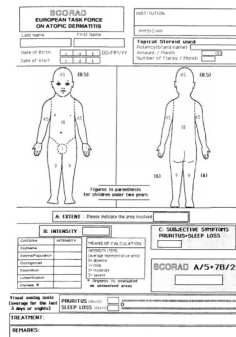
Plus 3 or more minor features:

- Xerosis
- Ichthyosis/palmar hyperlinearity/keratosis pilaris
- Immediate (type I) skin test reactivity
- Elevated serum IgE
- Early age of onset
- Tendency toward cutaneous infections (esp. *Staph. aureus* and *Herpes simplex*)/impaired cell-mediated immunity
- Tendency toward non-specific hand or foot dermatitis
- Nipple eczema
- Cheilitis
- Recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- Keratoconus
- Anterior subcapsular cataracts
- Orbital darkening
- Facial pallor/facial erythema
- Pityriasis alba
- Anterior neck folds
- Itch when sweating
- Intolerance to wool and lipid solvents
- Perifollicular accentuation
- Food intolerance
- Course influenced by environmental/emotional factors
- White dermographism/delayed blanch

2 Tools for the assessment of severity

2a The SCORAD Index – used in the guidelines

<https://www.karger.com/Article/Pdf/247298>



The image shows the SCORAD Index form, which includes a patient information section, a body diagram for scoring, and a calculation section. The body diagram shows the distribution of lesions on the face, neck, trunk, and limbs. The calculation section includes a table for scoring and a final score calculation.

2b The EASI scoring system – quick and easy for medical professionals

<https://eaiscore.com/>

2c The POEM score – for self-completion and/or proxy completion

<https://www.nottingham.ac.uk/research/groups/cebd/documents/methodological-resources/poem-for-self-completion-or-proxy-completion.pdf>

FIGURE 3 (Continued)

metabolic syndrome to Th-1 inflammation should be addressed. At present, US and Asian data indicate cardiometabolic diseases with gender-specific differences as a comorbidity of AD, while data from European patients do not support this.^{14,50–52}

As an example of multidisciplinary efforts, an Italian team created a patient questionnaire in order to detect type 2 inflammatory disorders and to guide subsequent multidisciplinary management.⁵³

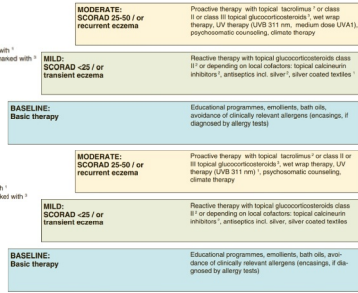
D)

Primary Care II: Additional Information

3 Stepwise treatment plan

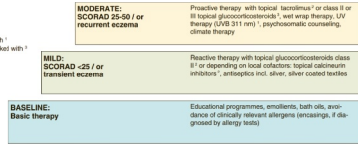
Treatment recommendation for atopic eczema: adult

- For every phase, additional therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with *
- Licensed indications are marked with †, off-label treatment options are marked with ‡



Treatment recommendation for atopic eczema: children

- For every phase, additional therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with †
- Licensed indications are marked with †, off-label treatment options are marked with ‡



4a Monitor therapy: VAS itch

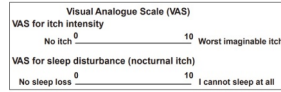
1.) On a scale of „no itch“ (left) to „worst imaginable itch“ (right), how was

your itch, on average, in the past 24 hours?

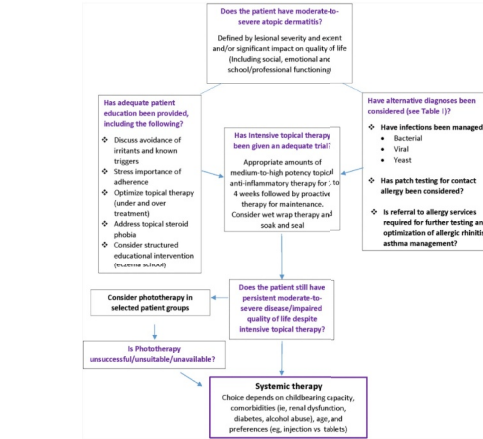
your worst itch in the past 24 hours?

- VAS 0 = no pruritus
- VAS < 3 = mild pruritus
- VAS > 3 - < 7 = moderate pruritus
- VAS > 7 - < 9 = severe pruritus
- VAS > 9 = very severe pruritus
- Validated in English, French, German, Italian, Polish, Russian, Spanish and Turkish <http://www.pruritussymposium.de/visualanaloguescale.html>

4b Monitor therapy: VAS nocturnal itch and sleep disturbance



5 Optimise treatment before switch



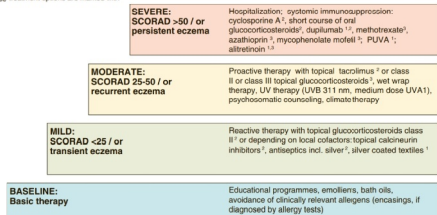
E)

Specialist: Additional Information

1 Treatment algorithm following national guidelines¹

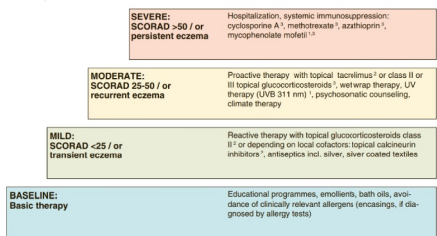
Treatment recommendation for atopic eczema: adult

- For every phase, additional therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with †
- Licensed indications are marked with †, off-label treatment options are marked with ‡



Treatment recommendation for atopic eczema: children

- For every phase, additional therapeutic options should be considered
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has insufficient effect
- Refer to guideline text for restrictions, especially for treatment marked with †
- Licensed indications are marked with †, off-label treatment options are marked with ‡



2 Special considerations for the paediatric population

2a Differential diagnoses

- Hyper IgE Syndrome
- Ommen Syndrome
- Wiskott-Aldrich Syndrome
- Selective IgA deficiency
- Cornell-Netherton Syndrome
- Peeling Skin Syndrome
- Phenylketonuria
- Biotin deficiency

2b When to test a child with AD for allergies?

- Immediate type systemic (IgE) reaction
 - Urticaria, vomiting, dyspnoea, hypotension – known food allergen
- Food induced urticaria – no delayed eczema flare
 - Known food allergen
- Peri-oral AD (infants)
 - Specific food intake – known food allergen
 - Not saliva irritated eczema
- Symptoms of respiratory rhinitis – asthma, disease
 - History of bronchiolitis
 - Urticaria – eczema flare (contact with known aero-allergen)

2c Which allergens to test (IgE) in a child with A.D.?

- Hen's egg, cow's milk, wheat, soya, nuts-tree nuts, fish (area dietary habits)
- Mites, molds, epithelia, grasses (area characteristics, family habits)

2d Parents' education

- Adequate hygiene practices / diapering
- Adequate textiles (not wool, nylon, long fiber textile)
- Staphylococcus aureus colonization / superinfection
- Vaccination program not to be postponed or avoided
- Climate, seasonal changes, sun exposure
- Swimming in chlorinated pools
- Tobacco smoke exposure
- Stress, conflicts in the family
- Trigger and/or factor of uncontrolled child's A.D.

2e Goals for antipruritic treatment

- To reduce
 - Sleep interruption / insomnia
 - Activities interruption / eating, playing
 - Resting interruption / not calming

3 Ophthalmologist referral letter

For the case of atopic dermatitis and involvement and impact on the eyes, the physician should write a letter to the Ophthalmologist stating that the patients suffers from severe atopic dermatitis and an affection of the eyes is suspected. Attach results of allergy testing to accompany the letter.

FIGURE 3 (Continued)

A holistic approach and an investment in integrated mental health services are required to address the higher risk for psychological stress, sleep, and mental health disorders, such as attention-deficit/hyperactivity disorder, anxiety, depression, disorder of behaviour, autism, and suicide.

4.3 | Rare but severe ocular comorbidities

Ophthalmological symptoms in patients with AD may be under detected and underestimated, all the more as patients can be asymptomatic.

To diagnose and treat ocular comorbidities in AD, ophthalmological symptoms should be detected by careful history taking of the patient. These could be itchy eyes, pain, tearing, red eyes, rubbing, and disturbance of vision.

To prevent ocular comorbidity, it is important to treat periorcular/eyelid eczema adequately to prevent corneal damage. Topical calcineurin inhibitors (TCI) are the first choice of treatment. Use of TCS on the eyelids can have deleterious effects on the incidence of ocular disease. In this case, high eye pressure should be screened because high corticosteroid intraocular pressure responsiveness is approximately 5% in the general population.⁵⁴

To treat conjunctivitis, dermatologists/allergologists can prescribe artificial tears and antihistamine/mast cell stabiliser eye drops (preferably without preservatives). Corticosteroid eye drops should preferably be prescribed by an ophthalmologist.

Patients should be referred promptly to an ophthalmologist in the case of pain, photophobia, or vision loss, all of which could indicate keratitis/uveitis. Patients should be referred non-acutely (i) in case of moderate-to-severe AD and eyelid eczema/facial involvement, which is difficult to control, (ii) if eyelid eczema requires repeated use of TCS or maintenance TCS, or (iii) if conjunctivitis during biological treatment is not responding to artificial tears and TCI on the eyelids, or (iv) before starting a systemic therapy. As dedicated ophthalmologists are sparse, it is important to formulate precise referral criteria.

Ocular comorbidity should be one of the factors to consider when choosing a specific systemic treatment.^{45–47}

4.4 | Topical treatment—Health care provision: Needs and limitations

Dysbiosis and the spectrum of sensitisation, especially mold (fungi), are important in the contemporary concept of barrier impairment in AD and influence the choice of topical treatment.^{55,56}

Topical treatment encompasses the preventative and supportive use of baseline therapeutics such as emollients and emollients 'plus', the latter containing saponins, flavonoids, riboflavins or bacterial lysates. Even for basic treatment with emollients, high costs can be a problem depending on economic status. In some places, there are also local cheaper alternatives that could be used potentially. In India, for example, coconut oil is often used but patients should be advised that low-quality substitutes may also have negative effects like contact allergy.

Topical treatment also includes anti-inflammatory substances such as corticosteroids and calcineurin inhibitors. For topical steroids, it is recommended to use primarily the more modern substances like mometasone, which have a lower level of cutaneous adverse events and do not lead to systemic levels.⁵⁷

The rationales, advantages, and limitations of treatment with topical therapies in AD are summarised in Table 1. Topical treatments are indicated as recommended by the guidelines and should be optimised before changing the type of therapy. The transition points from topical treatments have been laid out in the European guideline and in IEC recommendation papers.^{24,25,39,58} However, it must be noted that treating large areas of the body with topical treatment has a severe negative impact on the quality of life and can influence the decision to move for systemic care.

Access to drugs is mostly good but varies by country, for example, in some countries a limited use of TCI was noted. In addition, reimbursement systems differ between countries and can further limit effective treatment. Even if reimbursement is given, guideline compliance shows large gaps, mostly due to the physicians' prescribing patterns. Concerns from both, patients and physicians, about the adverse effects of corticosteroid can limit effective treatment. Regular training of primary care clinicians by specialists could help to close these gaps.

In conclusion, there is a clear differential need for topical treatment in AD with mostly preventive, curative, or supportive

TABLE 1 Rationale, needs and limitations for topical therapy in atopic dermatitis.

Rationale	<ul style="list-style-type: none"> • To prevent and improve barrier disruptions • To control inflammation • To restore and maintain the skin microbiome • To address specific problems such as itch, pain, superinfections, or exudation
Advantages	<ul style="list-style-type: none"> • Connection with the problem of barrier dysfunction • Efficiency when used adequately • Control of side effects • Flexible dosing and application modes • Versatility in including further compounds • General acceptance by most patients
Limitations	<ul style="list-style-type: none"> • Burden of time • No reimbursement from health insurances for basic therapy • High costs for some of the newer topical treatments
Needs	<ul style="list-style-type: none"> • Development of easy-to-use clinical scores to monitor treatment success as the validated scores such as SCORAD, EASI or DLQI are excellent in clinical trials but too time consuming for daily routine • Further criteria should be developed for decision making in step up or down in treatment: The objective and subjective burden, the patient's history, time course of the disease, the patient's preferences and response to topical treatment

reasons. There is a consensus about the criteria for using topical versus systemic treatment. Optimising treatment before switching is key. However, the current health care quality of AD with topical treatments is diverse and the benefits of topical treatments in individual patients are highly variable.

4.5 | Systemic treatments in AD

Most patients with mild-to-moderate AD respond adequately to optimised topical treatment and avoidance of exacerbating factors. The management of bacterial, viral and/or fungal skin infections is of major importance as they can be the cause of acute exacerbations of disease severity or resistance to treatment.

However, many patients may not have adequate disease control with topical treatment alone or in combination with phototherapy using UVB or UVA, which can be of value in selected cases. In these patients and those with moderate-to-severe AD, systemic therapy is needed to control skin inflammation. The decision when to start a systemic therapy can be difficult, given the known risks of traditional immunosuppressants, which may cause concern about infections, particularly during the COVID-19 pandemic.³⁹

The availability of systemic drugs is subject to country-specific differences as well as payment and out-of-pocket costs in the private versus general health care sections.

Off label drugs still play a role in the management of AD. However, licensed therapies should be considered first. Several new therapies approved for the treatment of AD are available, such as biologicals (dupilumab and tralokinumab) and JAK inhibitors (baricitinib, upadacitinib and abrocitinib). Besides, further new therapies targeting other pathogenic mechanisms such as IL31 (nemolizumab) are emerging.^{59–61}

The choice of systemic treatment in AD is dependent on the patients' age, efficacy, safety, comorbidities, and also the economic burden of the treatment (Table 2). Furthermore, specific concerns exist for some of the new agents and treating physicians should be familiar with the contraindications and appropriate laboratory follow up.

For certain patient subgroups, specific internationally published recommendations for systemic treatments exist, for example, for patients with comorbidities (e.g. asthma, rheumatoid arthritis), pregnancy, history of cancer, and planned vaccinations. Further subgroups require specific considerations, such as elderly patients and breastfeeding mothers.

Children and adolescents as a target group require special attention to safety aspects and for some substances specific adverse effects need to be considered, for example, for methotrexate. However, particularly in adolescents, the impact of AD on the quality of life is considerably high and may differ from other age groups.⁶² Furthermore, adequate disease control in children and

TABLE 2 Overview of currently licensed treatments for atopic dermatitis and/or other allergic comorbidities.

Drug	Licensed for atopic dermatitis	Licensed for allergic asthma	Licensed for chronic rhinosinusitis +/- nasal polyposis	Licensed for allergic rhinitis	Licensed for food allergies	Licensed for Other
Dupilumab	X Adults Children ≥6 years	X Adults Children ≥6 years	X Adults	-	-	-
Tralokinumab	X Adults	-	-	-	-	-
Baricitinib	X Adults	-	-	-	-	Adults with rheumatoid arthritis
Upadacitinib	X Adults Children ≥12 years	-	-	-	-	Adults with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis
Abrocitinib	X Adults	-	-	-	-	-
Methotrexate	-	-	-	-	-	Adults with rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, Crohn's disease
Cyclosporin A	X (>16 years in Germany and Austria)	-	-	-	-	Adults with rheumatoid arthritis, psoriasis, atopic keratoconjunctivitis

adolescents may affect the allergy march.⁶³ Fortunately, novel treatments, such as dupilumab, are now also available for pediatric patients.

4.6 | New and emerging treatments: Biologics

The ideal aim is complete control by modern treatment achieving symptom-free life while acknowledging that this cannot be easily achieved in a complex, chronic immune-mediated inflammatory disease. In that case, there must be a joint discussion between the physician and patient about what is the realistic treatment aim, for example, aiming for symptom-free subthreshold eczema as well as the avoidance of flare ups.

Applications of newly developed drugs in clinical studies or already in daily practice show substantial progress in the treatment of moderately-to-severely affected patients with AD not responsive to standard topical treatments with corticosteroids or calcineurin inhibitors alone. Moreover, novel treatment approaches generate new knowledge about the (anti)inflammatory effects of immune modulation in AD and the heterogeneity of patient subgroups, which may stimulate further innovations in this field.

When evaluating new therapies for AD, special importance is attached to the assessment of patient-related outcomes. For the future, drugs highly effective for symptoms such as pruritus with a good benefit/risk ratio, with the possibility of individual dosing, and a rapid effect on symptom improvement after initiation of therapy are desired.

Dupilumab was the first specific therapeutic monoclonal antibody approved for the treatment of AD in 2017. The AD TREAT Germany registry demonstrated that dupilumab to date is by far the most prescribed systemic drug for AD with proven efficacy.^{41,60,64,65} Since autumn 2020, three JAK inhibitors have been approved for the treatment of AD in Europe (baricitinib, upadacitinib and most recently abrocitinib).^{61,66} Moreover, the anti-IL-13 specific monoclonal antibody tralokinumab was approved for the treatment of AD in adults.⁶⁷ While dupilumab is approved for adults as well as children, the benefits and safety of monoclonal antibodies and JAK inhibitors in moderate-to-severe AD in children and adolescents are still under investigation.⁶⁸

Although anti-IgE treatment is effective in some patients with asthma, it has not been proven to be effective in patients with AD so far.^{69,70}

The efficacy of house dust mite (HDM) sublingual immunotherapy (SLIT) has been shown in patients with airway allergic diseases. Over the last years, several randomised controlled studies demonstrated that HDM SLIT represents an additional therapeutic tool for the treatment of mild-to-moderate AD in selected patients with comorbid-allergic rhinitis and/or asthma.^{71,72}

So far, it is still unclear what patients benefit most from which systemic therapy. The guidance on the treatment approach in patients with moderate-to-severe AD and those with comorbidities is an important future task. Many of the newly licensed as well as

emerging treatments have a positive effect not only on AD but also on atopic and non-atopic comorbidities.

Table 2 gives an overview of the currently licensed treatments for AD and/or other allergic comorbidities.

Short comparative trials are available; however, most treatments have not been compared head-to-head yet.⁵⁹ In acknowledgment of the rapidly increasing evidence for a variety of emerging new therapies, an international group of clinicians, scientists and patients has conducted a living systematic review and network meta-analysis to provide relative efficacy, safety and impact on quality of life for available treatments. The results are updated regularly and made easily accessible on the website www.eczematetherapies.com for patients and clinicians.⁷³

At present, no treat-to-target framework exists to guide the optimal use of systemic therapies in AD. As the current evidence-base for specific recommendations is still sparse, an international consensus framework was sought based on expert opinion and informed by extensive clinical experience. A clinical algorithm has been proposed to guide shared decision-making for systemic treatment, continuation, modification, or discontinuation in adults with moderate-to-severe AD. This work is intended to be a starting point and foundation to inform and stimulate a wider debate.⁵⁸

4.7 | AD in the pediatric population

Cohort studies demonstrate a cumulative incidence of 22.8% in children aged 0–6 years and an AD lifetime prevalence of 21.3% in adolescents and 34.1% in adults.^{3,74,75}

Special considerations in the pediatric population concern the complex interrelations between an evolving disease with different phenotypes and endotypes, a developing child, the maturation of skin, the immune system, and metabolism.

A correct diagnosis considering frequent and rare differential diagnoses needs to be ensured by a specialist when needed. Food allergies and immunodeficiencies must be considered in patients with severe and/or persistent courses, particularly in patients with an early onset. Children with severe and/or therapy-resistant AD in combination with high IgE levels and/or hypereosinophilia should be investigated for genetic inborn errors of immunity with the expertise of allergologists, immunologists, and geneticists.⁷⁶

Furthermore, parents' perceptions should be considered, treatment safety assessed by age, long-term disease control achieved, and comorbidities recognised early and prevented when possible. It is important to look at the complex interaction the disease has both on the family life as well as its impact on the life of the child itself when for instance at school.

Basic skin care and topical treatment should be chosen considering the safety, tolerability, hypoallergenic properties, and parent and child's acceptance. Pruritus control is an important therapy goal. A personalised written action plan and team-school training to build

self-confidence and support self-management should be provided for patients and caregivers.^{20,23}

Skin-barrier dysfunction can be apparent in the first weeks of life before the development of AD, suggesting that interventions to improve skin barrier function from infancy have the potential to prevent the skin condition.⁷⁷ Gentle skin care for newborns supports skin function and ongoing postnatal skin maturation. Hence, recommendations on bathing and skin moisturisation, umbilical cord and diaper area care, and sun protection should be given to parents by midwives, nurses, and physicians.⁷⁸ However, a Cochrane meta-analysis concluded that skin care interventions such as emollients during the first year of life in healthy infants are probably not effective in preventing AD. Further work is needed to understand whether different approaches to infant skin care might promote or prevent AD.^{79–81}

4.8 | Living with the disease

AD is a chronic disease with different grades of severity, and it needs a reassessment of diagnostic features since new triggers may evolve, and an adaptation of the therapy may be needed. Ideally, depending on the grade or severity of AD, a physician should be in regular contact with the patient. The patient should also be empowered as much as possible to treat their own disease according to the fluctuating needs or disease status, but at the same time is trained enough at regular visits to assess these changes and triggers sensibly. This also includes early advising of parents about the prognosis of the disease and allergy prevention, for example, not smoking and early disease detection.

4.9 | The role of the pharmacist

Pharmacists should play a role in improving the patient's adherence with therapy, to reinforce and emphasise physicians' messages, and to prevent prescription mistakes (e.g. misdosing, incorrect drug name, individual patient contraindications) and drug-drug-interactions.

Currently, pharmacists mainly counsel on moisturisers and over the counter medications. The training of pharmacists is crucial considering the-phobia of patients and pharmacists. Specifically trained dermatological 'speciality' pharmacists within a pharmacy team would be desirable, providing the support outlined in Figure 2C. The geographical variability of the resources and training will significantly affect the role the pharmacists play in AD treatment. In some countries, the role of an even highly specialised pharmacist in the context of systemic therapies is an important development.

5 | AN OUTLOOK FOR AD

While the AD-ICPs focus on the current situation, this concluding chapter aims at the future perspectives with potential implications for research activities.

5.1 | Limited resources

AD is increasing in prevalence in lower- and middle-income countries of Asia, Africa, Latin America, and the Middle East. Challenges include cost, access to care, and lack of specialists. Furthermore, most of the available diagnostic criteria and treatment guidelines are based on European and North American populations and only few trials report the ethnicity of the study population.⁸² Although AD presents similarly across racial and ethnic groups, some features may be different in patients with darker skin, as well as drug pharmacokinetics and adverse effects in different ethnicities are yet to be investigated. The unmet medical need for the management of AD in developing countries can be addressed by the training of specialists, improvement of access to and affordability of care.^{83,84} Furthermore, more financial support is needed for educational programs. This can save costs as well-educated patients can more easily control their disease.

5.2 | A personalised approach for AD patients

Despite its complex pathophysiology and variable clinical phenotype, AD is often considered a single disease and treated with a uniform approach. More tailored prevention and therapeutic strategies are being explored, such as by the BIOMAP Consortium, aiming to stratify AD patients according to their phenotype and endotype with the support of new biomarkers.^{85,86} Such a personalised approach may help to assign available and newly emerging drugs to those patients with the best benefit/risk ratio.²² Associations found using machine learning to perform deep phenotyping and identification of severity-associated factors might contribute to improving the monitoring of predisposed patients, and personalised disease management.⁸⁷

5.3 | Recent geopolitical developments, the impact of climate change on allergies and AD

Addressing climate change may be the greatest challenge and most impactful intervention for global health in the 21st century; at the same time, failure to do so could destroy all the progress that has been made in public health in recent decades.^{88–90} With regard to allergies, climate change affects the severity of symptoms and increases in incidence and prevalence through its impact on pollen counts: The pollen season is getting longer, pollen is more allergenic and new pollen such as ragweed are becoming native to Europe.^{91–93} Patients suffering from AD triggered by pollen are more likely to be affected by these consequences of climate change. Furthermore, increasing heat waves are likely to be a trigger for more eczema exacerbations. Of note, both low and high ambient temperatures can increase the risk of outpatient visits.⁹⁴ More exposure-response association analyses are needed to understand the effects of ambient temperature and eczema to develop preventive measures.

Furthermore, no data are available on the effect of heat on local and systemic treatment of atopic eczema.

5.4 | ICPs by digital harmonisation

As part of a patient-centred approach, digitally supported ICPs could shorten the time to diagnosis, guide the patient in implementing the stepwise treatment plan and collect feedback from patients. They could also facilitate shared decision making between specialists. The existing MASK air app is the optimal app to add to comorbidities and AD. As a future perspective, this app should be embedded in other disease management systems. In the near-term future, digital health solutions could be provided at the government level in the national and other frequent languages for nomadic working citizens.

AUTHOR CONTRIBUTIONS

Torsten Zuberbier: Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); visualization (equal); writing – review & editing (equal). **Amir Abdul Latiff:** Formal analysis (equal); methodology (equal); writing – review & editing (equal). **Xenofon Aggelidis:** Conceptualization (equal); data curation (equal); writing – review & editing (equal). **Matthias Augustin:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Radu-Gheorghe Balan:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Christine Bangert:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Lisa Beck:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Thomas Bieber:** Formal analysis (equal); writing – review & editing (equal). **Jonathan A. Bernstein:** Formal analysis (equal); writing – review & editing (equal). **Marta Bertolin Colilla:** Formal analysis (equal); writing – review & editing (equal). **Alejandro Berardi:** Formal analysis (equal); writing – review & editing (equal). **Anna Bedbrook:** Formal analysis (equal); writing – review & editing (equal). **Carsten Bindsvlev-Jensen:** Formal analysis (equal); writing – review & editing (equal). **Jean Bousquet:** Formal analysis (equal); writing – review & editing (equal). **Marjolein de Bruin-Weller:** Formal analysis (equal); writing – review & editing (equal). **Dayanne Bruscky:** Formal analysis (equal); writing – review & editing (equal). **Betul Buyuktiryaki:** Formal analysis (equal); writing – review & editing (equal). **Giorgio Walter Canonica:** Formal analysis (equal); writing – review & editing (equal). **Carla Castro:** Formal analysis (equal); writing – review & editing (equal). **Natia Chanturidze:** Formal analysis (equal); writing – review & editing (equal). **Herberto Jose Chong-Neto:** Formal analysis (equal); writing – review & editing (equal). **Chia-Yu Chu:** Formal analysis (equal); writing – review & editing (equal). **Leena Chularojanamontri:** Formal analysis (equal); writing – review & editing (equal). **Michael Cork:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Roberta F. J. Criado:** Formal analysis (equal); writing – review & editing (equal). **Laia Curto Barredo:** Funding acquisition (equal); writing – review &

editing (equal). **Adnan Custovic:** Formal analysis (equal); writing – review & editing (equal). **Ulf Darsow:** Formal analysis (equal); writing – review & editing (equal). **Arben Emurlai:** Formal analysis (equal); writing – review & editing (equal). **Ana de Pablo:** Formal analysis (equal); writing – review & editing (equal). **Stefano Del Giacco:** Formal analysis (equal); writing – review & editing (equal). **Giampiero Girolomoni:** Formal analysis (equal); writing – review & editing (equal). **Tanja Deleva Jovanova:** Formal analysis (equal); writing – review & editing (equal). **Mette Deleuran:** Formal analysis (equal); writing – review & editing (equal). **Nikolaos Douladiris:** Formal analysis (equal); writing – review & editing (equal). **Bruno Duarte:** Formal analysis (equal); writing – review & editing (equal). **Ruta Dubakiene:** Formal analysis (equal); writing – review & editing (equal). **Esben Eller:** Formal analysis (equal); writing – review & editing (equal). **Batya Engel-Yeger:** Formal analysis (equal); writing – review & editing (equal). **Luis Felipe Ensina:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Nelson Rosario Filho:** Formal analysis (equal); writing – review & editing (equal). **Carsten Flohr:** Formal analysis (equal); writing – review & editing (equal). **Daria Fomina:** Formal analysis (equal); writing – review & editing (equal). **Wojciech Francuzik:** Formal analysis (equal); writing – review & editing (equal). **Maria Laura Galimberti:** Formal analysis (equal); writing – review & editing (equal). **Ana M. Giménez-Arnau:** Formal analysis (equal); writing – review & editing (equal). **Kiran Godse:** Formal analysis (equal); writing – review & editing (equal). **Charlotte Gotthard Mortz:** Formal analysis (equal); writing – review & editing (equal). **Maia Gotua:** Formal analysis (equal); writing – review & editing (equal). **Michihiro Hide:** Formal analysis (equal); writing – review & editing (equal). **Wolfram Hoetzenecker:** Formal analysis (equal); writing – review & editing (equal). **Nicolas Hunzelmann:** Formal analysis (equal); writing – review & editing (equal). **Alan Irvine:** Formal analysis (equal); writing – review & editing (equal). **Carolyn Jack:** Formal analysis (equal); writing – review & editing (equal). **Ioanna Kanavarou:** Formal analysis (equal); writing – review & editing (equal). **Norito Katoh:** Funding acquisition (equal); writing – review & editing (equal). **Tamar Kinaciyan:** Formal analysis (equal); writing – review & editing (equal). **Emek Kocatürk:** Formal analysis (equal); writing – review & editing (equal). **Kanokvalai Kulthanan:** Formal analysis (equal); writing – review & editing (equal). **Hilde Lapeere:** Formal analysis (equal); writing – review & editing (equal). **Susanne Lau:** Formal analysis (equal); writing – review & editing (equal). **Mariana Machado Forti Nastri:** Formal analysis (equal); writing – review & editing (equal). **Michael Makris:** Formal analysis (equal); writing – review & editing (equal). **Eli Mansour:** Formal analysis (equal); writing – review & editing (equal). **Alexander Marsland:** Formal analysis (equal); writing – review & editing (equal). **Mara Morelo Rocha Felix:** Formal analysis (equal); writing – review & editing (equal). **Ana Paula Moschione Castro:** Formal analysis (equal); writing – review & editing (equal). **Eustachio Nettis:** Formal analysis (equal); writing – review & editing (equal). **J. F. Nicolas:** Formal analysis (equal); writing – review & editing (equal). **Audrey Nosbaum:** Formal analysis (equal); writing – review & editing (equal). **Mikaela Odemyr:** Formal analysis (equal); writing – review & editing

(equal). **Niki Papapostolou:** Formal analysis (equal); writing – review & editing (equal). **Claudio A. S. Paris:** Formal analysis (equal); writing – review & editing (equal). **Sushil Paudel:** Formal analysis (equal); writing – review & editing (equal). **Jonny Peter:** Formal analysis (equal); writing – review & editing (equal). **Prakash Pokharel:** Formal analysis (equal); writing – review & editing (equal). **Luis Puig:** Formal analysis (equal); writing – review & editing (equal). **Tamara Quint:** Formal analysis (equal); writing – review & editing (equal). **German Dario Ramon:** Formal analysis (equal); writing – review & editing (equal). **Frederico Regateiro:** Formal analysis (equal); writing – review & editing (equal). **Giampaolo Ricci:** Formal analysis (equal); writing – review & editing (equal). **Cristine Rosario:** Conceptualization (equal); formal analysis (equal); writing – review & editing (equal). **Cansin Sackesen:** Formal analysis (equal); writing – review & editing (equal). **Peter Schmid-Grendelmeier:** Formal analysis (equal); writing – review & editing (equal). **Esther Serra-Baldrich:** Formal analysis (equal); writing – review & editing (equal). **Kristina Siemens:** Conceptualization (equal); writing – original draft (equal); writing – review & editing (equal). **Cathrine Smith:** Formal analysis (equal); writing – review & editing (equal). **Petra Staubach:** Formal analysis (equal); writing – review & editing (equal). **Katarina Stevanovic:** Conceptualization (equal); project administration (equal); visualization (equal); writing – original draft (equal); writing – review & editing (equal). **Özlem Su-Küçük:** Formal analysis (equal); writing – review & editing (equal). **Gordon Sussman:** Formal analysis (equal); writing – review & editing (equal). **Simona Tavecchio:** Formal analysis (equal); writing – review & editing (equal). **Natasa Teovska Mitrevska:** Formal analysis (equal); writing – review & editing (equal). **Diamant Thaci:** Formal analysis (equal); writing – review & editing (equal). **Elias Toubi:** Formal analysis (equal); writing – review & editing (equal). **Claudia Traidl-Hoffmann:** Formal analysis (equal); writing – review & editing (equal). **Regina Treudler:** Formal analysis (equal); writing – review & editing (equal). **Zahava Vadasz:** Formal analysis (equal); writing – review & editing (equal). **Ingrid van Hofman:** Project administration (equal). **Maria Teresa Ventura:** Formal analysis (equal); writing – review & editing (equal). **Zhao Wang:** Formal analysis (equal); writing – review & editing (equal). **Thomas Werfel:** Formal analysis (equal); writing – review & editing (equal). **Andreas Wollenberg:** Formal analysis (equal); writing – review & editing (equal). **Ariana Yang:** Formal analysis (equal); writing – review & editing (equal). **Yik Weng Yew:** Formal analysis (equal); writing – review & editing (equal). **Zuotao Zhao:** Formal analysis (equal); writing – review & editing (equal). **Ricardo Zwiener:** Formal analysis (equal); writing – review & editing (equal). **Margitta Worm:** Formal analysis (equal); writing – review & editing (equal).

AFFILIATIONS

¹Institute of Allergology, Charité - Universitätsmedizin Berlin, Berlin, Germany

²Allergology and Immunology, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany

³Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

⁴Allergy Unit, 2nd Department of Dermatology and Venereology, National and

Kapodistrian University of Athens, University General Hospital "Attikon", Athens, Greece

⁵University Medical Center Hamburg-Eppendorf, Hamburg, Germany

⁶Institute for Health Services Research in Dermatology and Nursing, Hamburg, Germany

⁷Institutul Regional de Gastroenterologie si Hepatologie, Cluj-Napoca, Romania

⁸Department of Dermatology, Medical University of Vienna, Vienna, Austria

⁹University of Rochester Medical Center, Rochester, New York, USA

¹⁰University Hospital of Bonn, Bonn, Germany

¹¹Christine Kühne-Center of Allergy Research and Education, Davos, Switzerland

¹²University of Cincinnati College of Medicine, Cincinnati, Ohio, USA

¹³Hospital del Mar, Barcelona, Spain

¹⁴Instituto de Asma, Alergia y Enfermedades Respiratorias, Corrientes, Argentina

¹⁵MACVIA-France, Fondation Partenariale FMC VIA-LR, Montpellier, France

¹⁶Department of Dermatology and Allergy Centre, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital, University of Southern Denmark, Odense C, Denmark

¹⁷Division of Allergy and Immunology, Complexo Hospital de Clinicas Federal University of Paraná, Curitiba, Brazil

¹⁸Department of Dermatology/Allergology, National Expertise Center for Atopic Dermatitis, University Medical Center Utrecht, Utrecht, The Netherlands

¹⁹Federal University of Pernambuco, Recife, Brazil

²⁰Division of Pediatric Allergy, Koc University Hospital, Istanbul, Turkey

²¹Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy

²²Department of Dermatology, Hospital Universitario Austral, Universidad Austral, Buenos Aires, Argentina

²³Center of Allergy and Immunology, Tbilisi, Georgia

²⁴Department of Dermatology, National Taiwan University Hospital, Taipei, Taiwan

²⁵Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

²⁶Sheffield Dermatology Research, IICD, University of Sheffield, Sheffield, UK

²⁷Alergoskin Alergia e Dermatologia, Santo Andre, Brazil

²⁸Department of Dermatology, Centro Universitario FMABC, Santo Andre, Brazil

²⁹Hospital del Mar, Parc de Salut Mar, Barcelona, Spain

³⁰National Heart and Lung Institute, Imperial College, London, UK

³¹Department of Dermatology and Allergy Biederstein, Technische Universität München, Munich, Germany

³²Clinical Hospital Tetovo, Tetovo, North Macedonia

³³Hospital Universitario Austral, Pilar, Argentina

³⁴Allergy and Clinical Immunology, University of Cagliari, Sardinia, Italy

³⁵Section of Dermatology, Department of Medicine, University of Verona, Verona, Italy

³⁶Health Center Skoplje, Skoplje, North Macedonia

³⁷Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark

³⁸Hospital Santo Antonio dos Capuchos, Centro Universitário de Lisboa Central, Lisbon, Portugal

³⁹Department of Immunology and Allergology, Medical Faculty, Clinics of Chest Diseases, Vilnius University, Vilnius, Lithuania

- ⁴⁰Occupational Therapy Department, Faculty of Social Welfare and Health Sciences, University of Haifa, Haifa, Israel
- ⁴¹CPAlpha Clinical Research Center, Barueri – São Paulo, Brazil
- ⁴²St John's Institute of Dermatology, St Thomas' Hospital, London, UK
- ⁴³Center of Allergy and Immunology, Clinical State Hospital 52, Moscow Ministry of Healthcare, Moscow, Russian Federation
- ⁴⁴Division of Allergy and Immunology, Department of Dermatology, Venereology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany
- ⁴⁵Hospital Italiano de Buenos Aires, Buenos Aires, Argentina
- ⁴⁶Dermatology Department, Hospital del Mar, IMIM, Universitat Autònoma y Universitat Pompeu Fabra, Barcelona, Spain
- ⁴⁷D.Y. Patil University, Navi Mumbai, Maharashtra, India
- ⁴⁸Department of Dermatology, Hiroshima University Hospital, Hiroshima, Japan
- ⁴⁹Department of Dermatology, Kepler University Hospital, Linz, Austria
- ⁵⁰Department of Dermatology, University of Cologne, Cologne, Germany
- ⁵¹Clinical Medicine, Trinity College Dublin, Dublin, Ireland
- ⁵²Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada
- ⁵³Department of Dermatology, Kyoto Prefectural University of Medicine, Kyoto, Japan
- ⁵⁴Ghent University Hospital, Ghent, Belgium
- ⁵⁵Charité-Universitätsmedizin Berlin, Berlin, Germany
- ⁵⁶Faculdade de Medicina, Hospital das Clínicas, Instituto da Criança e do Adolescente, Universidade de São Paulo, São Paulo, Brazil
- ⁵⁷Division of Allergy and Immunology, Department of Clinical Medicine, University of Campinas, Campinas, Brazil
- ⁵⁸Salford Royal Foundation Trust - University of Manchester and Spire Manchester Hospital, Manchester, UK
- ⁵⁹AlergoLife Clinici, Rio de Janeiro, Brazil
- ⁶⁰Instituto da Criança, Rio de Janeiro, Brazil
- ⁶¹Department of Emergency and Organ Transplantation, School and Chair of Allergology and Clinical Immunology, University of Bari - Aldo Moro, Bari, Italy
- ⁶²Department of Clinical Immunology and Allergy, Lyon-Sud University Hospital, CIRI/INSERM U1111, Lyon, France
- ⁶³Service d'Allergologie et Immunologie Clinique, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France
- ⁶⁴Centre International de Recherche en Infectiologie, INSERM U1111, CNRS UMR 5308, UCBL1, ENS de Lyon, Lyon, France
- ⁶⁵EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium
- ⁶⁶President of the Swedish Asthma and Allergy Association, Stockholm, Sweden
- ⁶⁷Center Civil Service Hospital, Kathmandu, Nepal
- ⁶⁸Division of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa
- ⁶⁹Allergy and Immunology Unit, University of Cape Town Lung Institute, Cape Town, South Africa
- ⁷⁰Instituto de Alergia e Inmunología del Sur, Bahía Blanca, Buenos Aires, Argentina
- ⁷¹Allergia e Inmunología Section, Hospital Italiano Regional del Sur, Bahía Blanca, Buenos Aires, Argentina
- ⁷²Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
- ⁷³Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal
- ⁷⁴Department of Medical and Surgical Sciences DIMEC, University of Bologna, Bologna, Italy
- ⁷⁵Federal University of Paraná, Curitiba, Brazil
- ⁷⁶Department of Dermatology Allergy Unit, University Hospital of Zürich, Zürich, Switzerland
- ⁷⁷Christine Kèhne Center for Allergy Research and Education CK_CARE, Davos, Switzerland
- ⁷⁸King's College London, London, UK
- ⁷⁹St John's Institute of Dermatology, Guys and St Thomas' NHS Trust, London, UK
- ⁸⁰Department of Dermatology and Allergy, Hautklinik und Poliklinik der Universitätsmedizin, University Medical Center, Mainz, Germany
- ⁸¹Department of Dermatology, Faculty of Medicine, Bezmialem Vakıf University, Istanbul, Turkey
- ⁸²Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
- ⁸³Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
- ⁸⁴ReMedika General Hospital, Skopje, North Macedonia
- ⁸⁵Center for Comprehensive Inflammation Medicine, University of Lübeck, Lübeck, Germany
- ⁸⁶Allergy and Clinical Immunology, Holy Family Hospital, Nazareth, Israel
- ⁸⁷Environmental Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany
- ⁸⁸Universität Leipzig Medical Faculty, Leipziger Interdisziplinäres Centrum für Allergologie, Leipzig, Germany
- ⁸⁹Bnai-Zion Medical Center, Haifa, Israel
- ⁹⁰GA²LEN Network, Berlin, Germany
- ⁹¹University of Bari Aldo Moro, Bari, Italy
- ⁹²Department of Dermatology, Second Affiliated Hospital, Northwest Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China
- ⁹³Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
- ⁹⁴Department of Dermatology and Allergy, Ludwig-Maximilians-University, Munich, Germany
- ⁹⁵Department of Dermatology, Free University Brussels, University Hospital Brussels, Brussels, Belgium
- ⁹⁶Division of Allergy and Clinical Immunology of University of São Paulo, São Paulo, Brazil
- ⁹⁷Faculty of Medical Sciences of UNICAMP, São Paulo, Brazil
- ⁹⁸National Skin Centre, Singapore, Singapore
- ⁹⁹Department of Dermatology, First Hospital Peking University, Beijing, China
- ¹⁰⁰Medicina Interna y Alergología e Inmunología Clínica, Hospital Universitario Austral, Pilar, Argentina

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Torsten Zuberbier  <https://orcid.org/0000-0002-1466-8875>
 Xenofon Aggelidis  <https://orcid.org/0000-0003-1715-3022>
 Carsten Bindslev-Jensen  <https://orcid.org/0000-0002-8940-038X>
 Jean Bousquet  <https://orcid.org/0000-0002-4061-4766>
 Betül Buyuktiryaki  <https://orcid.org/0000-0003-1206-969X>
 Roberta F. J. Criado  <https://orcid.org/0000-0003-2482-3047>
 Ana M. Giménez-Arnau  <https://orcid.org/0000-0001-5434-7753>
 Eli Mansour  <https://orcid.org/0000-0001-6450-6930>
 Jonny Peter  <https://orcid.org/0000-0002-2658-0723>
 Zuotao Zhao  <https://orcid.org/0000-0002-9595-6050>
 Ricardo Zwiener  <https://orcid.org/0000-0001-9636-6741>
 Margitta Worm  <https://orcid.org/0000-0002-3449-1245>

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