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## POSITION STATEMENT

# ETFAD/EADV Eczema task force 2020 position paper on diagnosis and treatment of atopic dermatitis in adults and children

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## Abstract

Atopic dermatitis (AD) is a highly pruritic, chronic inflammatory skin disease. The diagnosis is made using evaluated clinical criteria. Disease activity and burden are best measured with a composite score, assessing both objective and subjective symptoms, such as SCORing Atopic Dermatitis (SCORAD). AD management must take into account clinical and pathogenic variabilities, the patient's age and also target flare prevention. Basic therapy includes hydrating and barrier-stabilizing topical treatment universally applied, as well as avoiding specific and unspecific provocation factors. Visible skin lesions are treated with anti-inflammatory topical agents such as corticosteroids and calcineurin inhibitors (tacrolimus and pimecrolimus), which are preferred in sensitive locations. Topical tacrolimus and some mid-potency corticosteroids are proven agents for proactive therapy, which is defined as the long-term intermittent anti-inflammatory therapy of frequently relapsing skin areas. Systemic anti-inflammatory or immunosuppressive treatment is a rapidly changing

<sup>†</sup>See Appendix section.

field requiring monitoring. Oral corticosteroids have a largely unfavourable benefit–risk ratio. The IL-4R-blocker dupilumab is a safe, effective and licensed, but expensive, treatment option with potential ocular side-effects. Other biologicals targeting key pathways in the atopic immune response, as well as different Janus kinase inhibitors, are among emerging treatment options. Dysbalanced microbial colonization and infection may induce disease exacerbation and can justify additional antimicrobial treatment. Systemic antihistamines (H1R-blockers) only have limited effects on AD-related itch and eczema lesions. Adjuvant therapy includes UV irradiation, preferably narrowband UVB or UVA1. Coal tar may be useful for atopic hand and foot eczema. Dietary recommendations should be patient-specific, and elimination diets should only be advised in case of proven food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Psychosomatic counselling is recommended to address stress-induced exacerbations. Efficacy-proven 'Eczema school' educational programmes and therapeutic patient education are recommended for both children and adults.

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### Conflicts of interest

AW has been a principal investigator, advisory board member or consultant for AbbVie, Almirall, Galderma, Hans Karrer, Leo Pharma, Lilly, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme, and received speaker honoraria from Chugai, Galderma, Leo Pharma, Lilly, L'Oréal, MedImmune, Pfizer, Pierre Fabre, Regeneron Pharmaceuticals, Inc., and Sanofi Genzyme. SCZ has been an advisor, speaker or investigator for Galderma, L'Oréal, La Roche Posay, Pierre Fabre, Procter and Gamble and Sanofi Genzyme. AT has been consultant or investigator for Pierre Fabre, Galderma, Novartis, Johnson and Johnson, Incyte, AbbVie, Modilac, Pfizer, Lilly, Arena, Bioderma and Sanofi. CP has been investigator or consultant for AbbVie, Almirall, Astellas, Boehringer, Bristol-Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen Cilag, Leo Pharma, Merck, Novartis, Pierre Fabre, Pfizer, Regeneron, Sanofi and UCB. JPT has been an investigator/advisor/presenter for AbbVie, Regeneron, Sanofi Genzyme, Leo Pharma, Eli Lilly & Co and Pfizer. MdB has been a principal investigator, consultant and advisory board member for AbbVie, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Leo Pharma and Pfizer. She has been an advisory board member and consultant for Eli Lilly and an advisory board member for Galderma and UCB. CV has received honoraria and research grants from Leo Pharma, Sanofi, Novartis, AbbVie and Eli Lilly. JS has received honoraria for lectures and advisory boards from AbbVie, Leo Pharma, Eli Lilly, Novartis, Pfizer, Pierre Fabre and Sanofi Genzyme. TW has received lecture or consultancy fees from AbbVie, Almirall, Astellas, Galderma, Janssen/JNJ, Leo Pharma, Lilly, Novartis, Pfizer and Regeneron/Sanofi. MJC is an Investigator and Consultant for Regeneron, Sanofi Genzyme, Pfizer, Leo, Galapagos, Novartis, Boots, L'Oréal, Dermavant, Menlo, Reckitt Benckiser, Oxagen, Johnson & Johnson, Hyphens, Astellas, Eli Lilly, AbbVie, Galderma and Procter & Gamble. BK has been a speaker, investigator or member of scientific advisory board for La Roche Posay, Beiersdorf, Procter and Gamble and Pierre Fabre. RFH reports being a consultant/advisor for Beiersdorf AG, Johnson & Johnson, Leo Pharma, Neubourg, Novartis Pharma AG, Nutricia, Pfizer Inc., Regeneron and Sanofi-Aventis as well as speaker for Beiersdorf AG, Leo Pharma, Neubourg, Novartis Pharma AG, Pierre Fabre Laboratories, Pfizer, Procter & Gamble, Regeneron and Sanofi-Aventis. MT has been an advisor, investigator or speaker for La Roche Posay, Leo Pharma, Pfizer, Pierre Fabre and Sanofi Genzyme. UD gave advice to or received an honorarium for talks or research grant from the following companies: ALK-Abello, Bencard, Meda, Novartis and Sanofi-Regeneron. SZ has performed consultancies for Sanofi Genzyme, Regeneron, Leo Pharma and Novartis; has lectured at educational events sponsored by Nutricia; and is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis. MD has been a principal investigator, speaker, advisory board member and/or consultant for Leo Pharma, AbbVie, Almirall, Lilly, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi Genzyme, Morphosys-Galapagos, Pierre Fabre and MEDA. LvK has been investigator, speaker or consultant for Pfizer, Sanofi, Leo Pharma and Eli Lilly. SB has been a principal investigator, advisory board member or consultant for Pierre Fabre, Bioderma, La Roche Posay, Sanofi Genzyme, AbbVie, Novartis, Janssen, Leo Pharma, Pfizer, Amgen and Lilly. AH received lecture or consultancy fees from Leo Pharma, Novartis, Pierre Fabre, Sanofi-Genzyme, Beiersdorf, Hans Karrer, Nutricia, Meda and Lilly and a travel grant from Janssen. UG reports no conflict of interest. DJH has been investigator, speaker or consultant for AbbVie, Eli Lilly, Incyte, Leo Pharma, MedImmune/AstraZeneca, Pfizer, Sanofi and Thermo Fisher. SW has received institutional research grants from Leo Pharma and L'Oréal; has performed consultancies for Sanofi Genzyme, Regeneron, Leo Pharma, Incyte, Lilly, AbbVie and Novartis; has lectured at educational events sponsored by Sanofi Genzyme, Regeneron, Leo Pharma, AbbVie and Galderma; and is involved in performing clinical trials with pharmaceutical industries that manufacture drugs used for the treatment of atopic dermatitis. LDR is a consultant, member of scientific

advisory boards and/ or received personal fees and non-financial support from Leo Pharma, Pierre Fabre, Sanofi Genzyme and Bioderma. DS has been an investigator, advisory board member or consultant for AbbVie, AstraZeneca, Galderma, Lilly, Pfizer, Roche Pharma and Sanofi Genzyme. JFS, JR and AS reports no conflict of interest.

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This article is the 4th edition of the European Task Force on Atopic Dermatitis (ETFAD) of the European Academy of Dermatology and Venereology (EADV) position paper. Like the earlier versions,<sup>1–3</sup> it communicates the experience, opinion and recommendation of the ETFAD on the current treatment and management options for atopic dermatitis (AD) in view of recently updated relevant guidelines,<sup>4,5</sup> position papers<sup>6</sup> and relevant original data from the point of view of care-giving expert physicians regularly involved in managing patients with AD. It is by intention neither a guideline, nor a systematic review, but a short expert opinion paper communicating clinically useful information for diagnosing and treating AD.

### Introduction and definitions

Atopic dermatitis (syn. atopic eczema, eczema, neurodermitis) is an inflammatory, chronically relapsing and intensely pruritic skin disease often occurring in families with atopic diseases (AD, food allergy, bronchial asthma or allergic rhinoconjunctivitis). The current understanding indicates that AD is a systemic T-helper (Th) 2-driven disease, in which the prevalence of atopic comorbidities is high, in particular in patients with moderate-to-severe AD.<sup>7</sup> From a clinical and histopathological standpoint, AD is an eosinophilic/spongiotic inflammation of the skin with characteristic age-dependent distribution patterns and morphology of lesions. With a prevalence of 2%–10%<sup>8</sup> in young adults and up to 20% in children, AD is one of the most common skin diseases. The varying aetiological concepts of this disease are mirrored by the different names that are or have been used, such as 'neurodermatitis', 'neurodermitis' and 'endogenous/constitutional eczema'.

Atopy can be defined as familial hypersensitivity of the skin and the mucosa to environmental substances, associated with increased production of immunoglobulin E (IgE) or altered pharmacologic reactivity.<sup>9</sup> The ETFAD defines atopy as the 'familial tendency to develop Th2 responses against common environmental antigens', which keeps both IgE-associated, extrinsic and non-IgE-associated, intrinsic subtypes<sup>10</sup> within the definition of atopy.

The atopic diseases are genetically linked, and the concordance in monozygotic twins is 80% vs. 30% in dizygotic twins.<sup>11</sup> Described genetic polymorphisms in AD involve mediators of atopic inflammation on different chromosomes, and some of these are also relevant for respiratory atopy. The strongest

association has been shown with mutations in the filaggrin gene also associated with ichthyosis vulgaris, highlighting the predisposing barrier defect in AD patients.<sup>12</sup> Concomitant ichthyosis vulgaris can be diagnosed clinically, and increased palmar hyperlinearity is a good indicator of filaggrin gene mutations.<sup>13</sup> In the first months of life, a yellowish layer of seborrhoeic, crusted scales on the scalp, known as 'cradle cap', may be the first presentation of AD and can be treated with emollients only. AD usually starts in the face, with middle face sparing, and on the extensor surfaces of the arms and legs of toddlers, as well as the trunk, sometimes showing extensive oozing and crusting. Later on, eczematous involvement of flexures, neck and hands predominates, accompanied by dry skin. The skin barrier dysfunction is reflected by an increased transepidermal water loss (TEWL).<sup>14</sup> Measuring TEWL with an evaporimeter and discussing the results with the patient will increase adherence to recommended emollient therapy. Lichenification is the result of scratching and rubbing, frequently at night-time. The prurigo type of AD is associated with predominant excoriated, nodular and lichenified lesions. Exacerbations often start as increased itch without visible skin lesions, followed by erythema, papules and infiltration. As histopathologic features are not specific for AD, routine histology is not useful for diagnosing AD, but may help to rule out differential diagnoses, such as cutaneous T-cell lymphoma in adults.<sup>3</sup>

In the absence of a specific diagnostic laboratory marker, AD is diagnosed clinically. The diagnostic power of an experienced clinician is superior to all diagnostic criteria available, but standardized criteria are needed for epidemiological research, as well as for inclusion criteria for clinical trials. Most diagnostic criteria are based on cutaneous signs of atopy.<sup>9,15</sup> Hanifin and Rajka's criteria include pruritus, typical morphology and distribution, chronic or chronically relapsing course, and atopic personal or family history (3 of 4 necessary), in addition to 3 minor criteria among a list of 21.<sup>15</sup> According to the UK working party criteria, itchy skin changes have to be diagnosed in the last 12 months, in addition to at least three of the following criteria: onset of the disease under the age of two years, history of involvement of skin folds, generalized dry skin, other atopic diseases and visible flexural eczema.<sup>16</sup>

Atopic dermatitis has a profound impact on all dimensions of the patient's life.<sup>17,18</sup> Moderate-to-severe AD is associated with depression, anxiety, reduced quality of life, impaired self-esteem

and suicide.<sup>19</sup> The social impact of moderate-to-severe AD is high and similar to the one of psoriasis, chronic obstructive bronchitis, cardiovascular disease and diabetes.<sup>20</sup>

Management of acute exacerbations (flares) of AD is a therapeutic challenge, as it requires efficient short-term control of acute symptoms, without compromising the overall management plan that targets long-term stabilization, flare prevention and avoidance of side-effects. Exacerbation may sometimes uncover relevant provocation factors, such as underlying allergies or infection. Consequently, the initial workup must include a detailed inquiry on the circumstances of the flare, and a careful dermatologic examination including lymph nodes, orifices and all skin folds. Professional attitude in face of exacerbated disease is setting the stage for future adherence.<sup>21</sup> Patients often have their own beliefs about the origin of their flare, but disparaging remarks at this time will only increase patient or parental frustration with conventional medicine. Patient fears regarding treatment side-effects must be taken seriously with a compassionate attitude. Therapeutic patient education is an extremely helpful tool to address patient beliefs and questions regarding disease and treatment.<sup>22</sup>

### Assessment of disease activity

As atopic dermatitis is a chronic disease, long-term management strategies are essential to consider. Consensus definitions for management procedures are necessary.<sup>23</sup> In clinical trials, three methods have been used to assess long-term control: repeated measurement of AD outcomes, amount of medication used and recording of AD flares/remissions.<sup>24</sup>

The notion of intolerance or resistance to topical treatments is a clinically meaningful soft term for inadequate AD improvement using potent topical corticosteroids (TCS) with intolerable long-term side-effects. As quantitative rules for prescription of topicals are rarely applied, it is difficult to refer to an upper limit to define resistance.<sup>3</sup> Very often, patients apply too little amounts of TCS leading to the perception of a lack of effect.

Overall disease activity should assess both objective and subjective symptoms, as both contribute to clinical severity.<sup>3</sup> This can be achieved with the SCORAD index.<sup>25</sup> Mild AD corresponds to SCORAD levels below 25 and severe AD to SCORAD levels above 50.<sup>26</sup>

Flare is a clinically meaningful term difficult to delineate.<sup>27</sup> Repeated measurements and arbitrary cut-offs of an existing severity scale, such as SCORAD,<sup>25</sup> measured at sequential intervals by physicians, have been used most frequently in the past.<sup>27</sup> However, defining flares based on the intensity of itch is difficult, as the level of tolerance to pruritus can vary largely.<sup>3</sup> Some patients with highly lichenified lesions report only moderate pruritus and insomnia. The amount of medication used by the patient can be measured to detect

variations or flares. Novel tools for patient use like the patient-oriented (PO) validated scoring system PO-SCORAD may detect changes in signs and symptoms.<sup>28</sup> A valid, reliable and feasible flare definition acceptable for all clinical and research settings has still not been consented.<sup>27</sup> The ETFAD definition of flare is 'acute, clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention' (see Table 1 for ETFAD definitions). Primary clinical outcome measures used in recent development programmes include the achievement of clear or almost clear skin (investigator global assessment of 0 or 1) or a 75% improvement in severity scores such as 'Eczema Area and Severity Index' (EASI) or SCORAD.<sup>29</sup> In addition, clinically relevant improvement in itch, as defined by a 3- to 4-point improvement in the 10-point itch numerical rating scale, is desirable.

Maintaining a long-term remission is a shared objective in chronic disorders. A widely accepted and uniform nomenclature would help to compare data. Long-term remission without lesions and treatment is usually synonym of cure, but the time without intervention that may correspond to such a situation is still to be defined. Remission achieved by the avoidance of irritants and allergens with sole emollient use is not comparable to remission under immunosuppressive agents or biologics (Table 1). Other proposals come from asthma management (weeks with complete control/ weeks with good control) or from pragmatically oriented judgement (increase in treatment, medical visit or call).<sup>30</sup> Kaplan–Meier diagrams comparing flare-free percentages of study populations using study drug and control for 1 year (or at least 3 months) is a clinically meaningful visualization for flare prevention studies.<sup>3</sup> Data extraction of 'percent patients flared at study end' from treated patients may produce misleading meta-analysis results,<sup>31</sup> whereas prolongation of time to first flare in 50% of treated vs untreated patients, or comparing the percentage of flare-free patients at a fixed time (e.g. 12 weeks), is recommended.<sup>32</sup> Long-term control scores for use in clinical trials have recently been developed by international teams.<sup>33</sup>

### Basic therapy for atopic dermatitis and skincare

Since AD is a chronic condition, treatment has to be planned with a long-term perspective and special attention must be given to long-term safety aspects.

### Cleansing

The skin must be cleansed thoroughly, but gently and carefully to get rid of crusts and mechanically eliminate bacterial contaminants, especially in the case of bacterial superinfection. Cleansers with or without antiseptics in non-irritant and low allergenic formulas may be used in various galenic forms such as syndets or aqueous solutions. As the duration of action of some antiseptics is very limited, mechanical cleansing is probably more important.<sup>34</sup> The pH should be in a physiological cutaneous

**(a) Treatment of atopic dermatitis: adult**

- For every grade, *additional* therapeutic options are given
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has no effect
- Refer to full text for restrictions, especially for treatment marked with <sup>1</sup>
- Licensed indication are marked with <sup>2</sup>, off-label treatment options are marked with <sup>3</sup>

<b>SEVERE:</b> <b>SCORAD &gt;50 / or persistent eczema</b>	Hospitalization; short course of cyclosporin A <sup>1,2</sup> , dupilumab <sup>2</sup> , short course of oral glucocorticosteroids <sup>1,2</sup> ; longer course of systemic immunosuppression: methotrexate <sup>3</sup> , azathioprin <sup>3</sup> , mycophenolate mofetil <sup>3</sup> ; PUVA <sup>1</sup> ; alitretinoin <sup>1,3</sup>
<b>MODERATE:</b> <b>SCORAD 25-50 / or recurrent eczema</b>	Proactive therapy with topical tacrolimus <sup>2</sup> or class II or class III topical glucocorticosteroids <sup>3</sup> , wet wrap therapy, UV therapy (UVB 311 nm, medium dose UVA1), psychosomatic counseling, climate therapy
<b>MILD:</b> <b>SCORAD &lt;25 / or transient eczema</b>	Reactive therapy with topical glucocorticosteroids class II <sup>2</sup> or depending on local cofactors: topical calcineurin inhibitors <sup>2</sup> , antiseptics incl. silver <sup>2</sup> , silver coated textiles <sup>1</sup> topical crisaborole <sup>3</sup>
<b>BASELINE</b> <b>Basic therapy</b>	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

**(b) Treatment of atopic dermatitis: children**

- For every grade, *additional* therapeutic options are given
- Add antiseptics / antibiotics in cases of superinfection
- Consider compliance and diagnosis, if therapy has no effect
- Refer to full text for restrictions, especially for treatment marked with <sup>1</sup>
- Licensed indication are marked with <sup>2</sup>, off-label treatment options are marked with <sup>3</sup>

<b>SEVERE:</b> <b>SCORAD &gt;50 / or persistent eczema</b>	Hospitalization; dupilumab <sup>1,2</sup> ; course of systemic immunosuppression: cyclosporin A <sup>3</sup> , methotrexate <sup>3</sup> , azathioprin <sup>3</sup> , mycophenolate mofetil <sup>1,3</sup>
<b>MODERATE:</b> <b>SCORAD 25-50 / or recurrent eczema</b>	Proactive therapy with topical tacrolimus <sup>2</sup> or class II or class III topical glucocorticosteroids <sup>3</sup> , wet wrap therapy, UV therapy <sup>1</sup> (UVB 311 nm), psychosomatic counseling, climate therapy
<b>MILD:</b> <b>SCORAD &lt;25 / or transient eczema</b>	Reactive therapy with topical glucocorticosteroids class II <sup>2</sup> or depending on local cofactors: topical calcineurin inhibitors <sup>2</sup> , antiseptics incl. silver <sup>2</sup> , silver coated textiles <sup>1</sup> topical crisaborole <sup>3</sup>
<b>BASELINE</b> <b>Basic therapy</b>	Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)

**Figure 1** The treatment recommendations according to the ETFAD member consensus for adults (a) and children (b) based on the severity of the disease

range around 5–6, but if possible, lower pH products are generally good for the skin barrier. A small randomized study did not show any difference in bathing twice weekly or everyday with

respect to AD severity,<sup>35</sup> as long as hydration of skin is managed after the bath. However, longer duration of the bath is associated with worsening of the symptoms.<sup>36</sup>

**Table 1** Definitions of descriptive items for the management of AD

<b>Flare:</b> Acute, clinically significant worsening of signs and symptoms of atopic dermatitis requiring therapeutic intervention.
<b>Instrument:</b> A unidimensional or multidimensional scoring system used to measure relevant items of a disease. The EASI, objective SCORAD, POEM and DLQI are validated instruments for signs, symptoms or quality of life of AD, whereas the SCORAD is a validated composite score assessing both signs and symptoms of AD.
<b>Intolerance to topical treatment:</b> Patient's opinion after at least 2 weeks of therapy with a new topical treatment, because of worsening of lesions or any difficulty to apply the drug (ointment not supported, pain, burning or any uncomfortable sensation).
<b>Items:</b> Measurable disease-related features can be either or both signs and symptoms.
<b>Proactive therapy:</b> Long-term, low-dose intermittent application of anti-inflammatory therapy to the previously affected skin, together with an ongoing emollient treatment of unaffected skin.
<b>Remission/Control:</b> Period without flare of at least 8 weeks without anti-inflammatory treatment (irritant/allergen avoidance and emollient use not included).
<b>Complete remission:</b> If using basic treatment (avoidance, emollients)
<b>Incomplete remission:</b> If using moderate treatment, topical corticosteroids or calcineurin inhibitors less than 30 g/month in children and less than 60 g/month after 15 years of age
<b>Control:</b> If using major treatment including phototherapy or immunosuppressants
<b>Severity of disease:</b> The overall impact of signs and symptoms of AD on a patient, which requires assessment with a composite score.
<b>Mild disease:</b> If SCORAD is <25
<b>Moderate disease:</b> If SCORAD is $\geq 25$ and <50
<b>Severe disease:</b> If SCORAD is $\geq 50$
<b>Sign:</b> A disease-related item captured by an observer. It has the potential to be objective and reproducible. Signs of AD may be assessed by EASI and objective SCORAD.
<b>Symptom:</b> A disease-related item captured by a patient. It is by definition subjective. Most symptoms mirror signs or other symptoms. Symptoms of AD may be assessed by POEM.
<b>Resistance to topical treatment:</b> Physician's opinion of a situation with unchanged or aggravated clinical score after at least 2 weeks of appropriately dosed and performed treatment.

The most important aspect of washing in AD is the avoidance of all harsh detergents and alkaline soap. The alternatives include emollient wash products (bath oils, shower emollient wash products) or using a leave-on emollient cream as a wash product.

Emollient bath additives for the treatment of childhood eczema showed no clinical benefit if used in addition to using leave-on emollients as a soap substitute.<sup>37</sup> The latter combination is rarely used in reality. The ideal is to let patients choose which emollient wash products they prefer, as this will be the one they will use. Topical emollients are preferentially applied immediately after a bath or a shower following gentle drying when the skin is still slightly humid, which is known as 'soak-and-seal' technique.<sup>34</sup> Although bathing seems very important, there is lack of good evidence to prove its effectiveness or specific parameters of use.

The ETFAD recommends regular bathing or showering in warm but not hot water about 2–7 times per week with very mild surfactant and emollient-based wash products in a 'soak-and-seal' approach.

### Emollient therapy

Atopic dermatitis is associated with skin barrier anomalies that facilitate an easier allergen penetration into the skin with an increased proneness to irritation and subsequent cutaneous inflammation. A lack of important stratum corneum intercellular lipids and an inadequate ratio between lipid compounds (cholesterol, essential fatty acids, ceramides), as well as filaggrin defects,<sup>12</sup> enhance TEWL. This leads to epidermal micro-fissuring, which may also cause direct exposure of Langerhans cell dendrites as well as nerve endings to the environment. A better molecular and biochemical knowledge on this predisposing background should provide access to barrier improving topical agents. The use of high-quality emollients can be cost-effective because they prevent the development of flares and the need for anti-inflammatory TCS and TCI.<sup>38</sup> Nevertheless, if an acute flare does occur, it is better to treat with anti-inflammatory topicals first as outlined below, instead of applying emollients to acute inflamed lesions.<sup>39,40</sup>

Emollients are not always beneficial, as some can lead to other skin sensory adverse events such as burning, stinging or pruritus, especially if the emollients are used on inflamed skin. About 1/3 of adult AD patients have developed contact allergies to ingredients of their emollients and type IV sensitization to emulsifiers, preservatives and fragrances being the most common.<sup>41</sup> In patients with this problem, it is best to use the simplest emollient ointment formulations with the smallest number of ingredients.

By tradition, emollients are defined as topical treatment with vehicle-type substances lacking active ingredients. Most of them contain a humectant (promoting stratum corneum hydration, such as urea or glycerol) and an occludent (reducing evaporation, such as petrolatum).<sup>4</sup> Urea is known to significantly reduce the risk of AD relapse.<sup>38</sup>

Several non-medicated products for topical treatment of AD contain putative active ingredients, but are neither fulfilling the definition of nor needing a licence as a topical drug. These products, referred to as 'emollients plus' by the European guideline, may contain, for example, flavonoids such as licochalcone A, saponins and riboflavins from protein-free oat plantlet extracts, bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* species, or a synthetic derivative of menthol such as menthoxypropanediol.<sup>4,42</sup> Emollients containing potentially allergenic plant proteins from peanut, oat or wheat should be avoided in children before the age of 2,<sup>43</sup> whereas protein-free plant extracts are apparently safe to use.<sup>44</sup>

The ETFAD recommends the daily use of liberal amounts of emollients, at least 30 g/day or 1 kg/month for an adult, which should preferentially be applied in a 'soak-and-seal' technique (Fig. 1).

### Primary prevention

Primary prevention targets the general or an at-risk population with preventive measures, if there is still no evidence of disease.

Emollients have recently been recommended for primary prevention of AD,<sup>45</sup> but there are conflicting data. On one hand, two pilot randomized trials showed a 32% and 50% relative risk reduction in incident AD by the daily use of emollients from birth in neonates who are at high risk of developing AD.<sup>46–48</sup> On the other hand, two recently published larger and longer trials with a less stringent intervention did not confirm these effects of emollients.<sup>49,50</sup> Though emollients are a mainstay of AD treatment, the role for primary prevention of AD is unclear at present.

Probiotics (inactivated bacteria) and prebiotics (fibres that can promote the growth of certain bacteria in the gut) have been studied for primary prevention of AD during pregnancy or in neonates, but older data were essentially inconclusive. A diagnosis of AD is associated with a decreased diversity of neonates' gut microbiota.<sup>51</sup> A new Cochrane systematic review and meta-analysis of 21 studies issued the recommendation that a mixture of probiotic supplementation given to the mother during pregnancy and continued, while breastfeeding would be most efficacious in reducing the risk of incidence of AD in children.<sup>52,53</sup>

The ETFAD does not give a recommendation for any dietary and lifestyle changes aiming at primary prevention of AD, because the quality of data is not sufficient to issue a sustainable recommendation for any of the interventions studied.

### Avoidance strategies based on a diagnosis of allergy

Atopic dermatitis is associated in particular with immediate but also delayed-type hypersensitivity against environmental allergens. Among food allergens, cow's milk, hen's egg, wheat, soya, tree nuts and peanuts are most frequently associated with AD exacerbation in infants and toddlers. In older children, adolescents and adults, pollen-related food allergies should be taken into account.<sup>54</sup> Irritant factors comprising chemicals and physical agents may complicate the course of the disease. Finally, contact sensitization to chemicals, drugs, plants or metals is as frequently found in AD as in non-atopic individuals and may complicate the clinical severity by overlying allergic contact dermatitis.<sup>55</sup> Diagnosing the individually relevant trigger factors for AD is more challenging than diagnosing the disease.

The ETFAD recommends an allergy workup for moderate-to-severe AD patients, which may include serum IgE, skin prick tests and patch tests for contact sensitization to ingredients of emollients and topical anti-inflammatory agents, depending on the individual history. Mild patients may be tested depending on clinical suspicion.

### Food allergens

About one-third of children with a moderate-to-severe AD have an associated food allergy.<sup>56</sup> It is a common misconception that

food allergy would be causative in the setting of AD. Parents must be warned that general elimination diets are not recommended,<sup>57</sup> and can be detrimental.<sup>58</sup> In AD children with proven food allergy, good skincare is also the mainstay of treatment, but identifying and avoiding trigger factors are important.<sup>57</sup>

Sensitizations to foods can be identified by means of in vivo tests (skin prick tests, prick-prick tests) and in vitro tests (serum specific IgE). A positive test indicates IgE-mediated sensitization, but may have poor correlation with clinical responses.<sup>59</sup> In addition, atopy patch tests proved to be useful for studying delayed food-related skin responses.<sup>60</sup>

A skin prick test (SPT) with food allergens (i.e. cow's milk, eggs, wheat, soya, peanut) is suggested in children <5 years with moderate-to-severe AD that is persistent in spite of optimized management and topical therapy. Food allergy is less common in older age groups. Tests are recommended when food allergy is suspected.

In vitro tests (i.e. specific IgE testing) are valuable when SPT cannot be applied because of *urticaria factitia* (urticarial dermographism), UV- and drug-induced skin hypo-reactivity or lack of compliance for SPT in infants.<sup>61</sup> Moreover, in vitro data of specific IgE to food allergens allow better quantitative grading of sensitization, which helps to estimate the probability of the risk of a clinical reaction and offers the opportunity to test single recombinant allergens, which may have a better diagnostic specificity than testing with food extracts. Importantly, skin prick test reactivity to foods seems to decrease during the first 7 years, whereas specific IgE against food allergens tend to increase.<sup>62</sup>

The atopy patch test (APT) for food allergens has been standardized for selected food and aeroallergens,<sup>60,63</sup> but preparations are expensive, not adequately reimbursed and also not approved for routine diagnosis by the authorities.<sup>60</sup> As a pragmatic alternative, the APT may be performed with self-made food material using large test chambers for 48–72 h, but these test materials are not standardized.<sup>64</sup> Whereas immediate-type reactions are associated with SPT positivity, delayed-type reactions are related to positive responses to APT.<sup>65</sup> However, food challenge cannot be replaced by patch testing.

The best method to prove clinically significant allergy is the double-blind placebo-controlled food challenge.<sup>61</sup> In clinical reality, elimination and reintroduction of a certain food after a reliable history can be sufficient. Oral challenging of AD patients with foods may induce early reactions such as urticaria, gastrointestinal or respiratory symptoms usually occurring within 30–120 min after allergen administration, or eczematous late-phase responses after 18–48 h. About 45% of oral food challenges result in both immediate and delayed reactions, whereas 12% showed worsening of eczema only.<sup>66</sup> The personal history has a low predictive value (30%) for oral challenge-induced late reactions, as opposed to 80% for immediate reactions.<sup>66</sup>

The ETFAD recommends that an elimination diet for AD should not be based on type I sensitization detected by blood or

skin prick tests, but on a reliable history followed by elimination and reintroduction of suspected food or an oral food challenge if this is feasible.

### Aeroallergens

Clinical observations and experimental studies indicate that aeroallergens are relevant trigger factors in AD patients.<sup>67</sup> Exacerbations of eczematous lesions after skin contact or inhalation have been described, but studies on allergen avoidance strategies show conflicting results.<sup>68</sup> Routine diagnostic workup of suspected allergy to aeroallergens includes detection of specific IgE by means of skin prick tests or *in vitro* IgE assays. However, both techniques have a low predictive value.

Atopy patch test (APT) with aeroallergens targets the cellular component of AD,<sup>63</sup> and has been performed with house dust mites, pollen and animal dander, obtaining different positivity rates (15%–100%) according to patch test materials and modalities.<sup>60</sup> On the basis of the history of aeroallergen-triggered AD flares, APTs proved to have higher specificity and lower sensitivity than the above-mentioned tests<sup>63</sup> and may detect sensitization in skin prick test negative, ‘intrinsic’ AD patients.<sup>65</sup>

Unfortunately, standardized aeroallergen preparations are not available for routine testing in APT so far. As still no feasible standard procedure for provocation of eczema in aeroallergen-mediated AD exists, specific avoidance strategies should be considered for highly sensitized patients with chronic, moderate-to-severe disease on a patient individual basis (Table 2).

### Contact allergy

Contact allergy may be detected in 40%–65% of AD patients and cause worsening of their skin lesions.<sup>69</sup> Factors favouring allergic contact dermatitis in AD patients include the prolonged and repeated exposure to ingredients of topical treatments, along with increased skin barrier penetration.<sup>70</sup> Emulsifiers, fragrances, preservatives, corticosteroids and other components of topical treatment preparations are the most relevant substances to be tested.<sup>41,69</sup> In addition, contact allergy to compositae plants should be considered, e.g. when severe facial eczema is observed during the summer months.<sup>71</sup> Children with AD who have long-lasting moderate-to-severe hand or foot dermatitis should always be patch-tested to evaluate whether they have an allergic contact dermatitis.<sup>72</sup> Patch testing of AD patients can be tricky, as Th2 inflammation may suppress contact allergy, which in turn requires physicians to test when the AD is under control.<sup>73</sup> Patch testing should be considered before systemic intervention is planned.<sup>74</sup> Patch testing of occupational allergens is discussed in a separate chapter below.

The ETFAD suggests setting a low threshold for performing patch tests with a standard series and components of topical treatment preparations in AD patients. In addition, patch testing is recommended in AD patients with recalcitrant disease,

**Table 2** List of aggravating factors and counselling for AD patients

- Clothing: Avoid skin contact with irritating fibres (wool, large fibre textiles). Do not use tight and too warm clothing to avoid excessive sweating. New non-irritating clothing, designed for AD children and adults, and especially silver-coated textiles are encouraged
- Tobacco: avoid exposure
- Cool temperature in bedroom and avoid too many bed covers
- Increase emollient use with cold weather
- Avoid exposure to herpes sores. Urgent visit if flare of unusual aspect
- Vaccines: normal schedule in non-involved skin, including egg-allergic patients (see text)
- Sun exposure: no specific restriction with careful use. Usually helpful because of anti-inflammatory effect and improvement of epidermal barrier. Encourage summer holidays in high altitude or at beach resorts
- Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool
- Food allergens
  - a Maintain breastfeeding until four months if possible; include all foods recommended for the given ages after 4 months, unless the child develops allergy symptoms or sensitization has been shown
  - b Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food
  - c Some patients show improvement by avoiding foods cross-reactive to pollen (e.g. birch pollen)
- Indoor aeroallergens
- House dust mites
  - a Use adequate ventilation of housing. Keep the rooms well-aerated even in winter
  - b Avoid wall to wall carpeting
  - c Remove dust with a wet sponge
  - d Vacuum with an adequate filtered cleaner once a week floors and upholstery
  - e Avoid soft toys in bed (cradle), except washable ones
  - f Wash bed sheets at a temperature higher than 55° every 10 days
  - g Bed and pillow encasings in Gore-Tex or similar
- Furred pets: Advice to avoid cats but not dogs preventively. If allergy to furred pets is demonstrated, be firm on avoidance measures
- Pollen: In sensitized individuals, close windows during peak pollen season on warm and dry weather and restrict if possible stays outdoors. Aeration at night and early in the morning or by rainy weather. Avoid exposure to risk situations (lawn mowing). Pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen.

atypical localization or aggravation without known cause, especially when systemic intervention is considered.

### Topical anti-inflammatory treatment

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application.<sup>2</sup> Topical treatment should be applied on hydrated skin if possible, especially when using ointments. If emollients and anti-inflammatory topical preparations must be applied to the same location, the cream formulation should be applied first and only 15 min later the ointment formulation. Even without wet wraps, topical therapy is time-consuming: patients should plan 30 min for one session. One well-conducted treatment per

day is usually sufficient; oozing AD may require a few days with higher treatment frequency.<sup>16</sup>

### Wet-wrap treatment

Children and adults with acute, oozing and erosive lesions sometimes do not tolerate standard topical application and should be treated with 'wet wraps' first until oozing stops.<sup>34</sup> Wet-wrap dressings with diluted TCS (e.g. 1 : 3 for class II and 1 : 5 for class III) are applied for up to 14 days (usually 3 days are sufficient) and are a safe crisis intervention treatment, with temporary systemic bioactivity of the corticosteroid as the only reported serious side-effects.<sup>75,76</sup> Specialized nurse care is desirable to monitor wet-wrap treatment and to guide caregivers and patients, as it is done in eczema schools.<sup>77</sup>

The ETFAD recommends wet-wrap treatment for AD patients in flare, or with acute, oozing and erosive lesions.

### Corticosteroids

Topical corticosteroids (TCS) are still the first-line anti-inflammatory treatment option in AD.<sup>5</sup> There are different strengths of TCS (mild, moderate, potent or super-potent) and different formulations (creams, ointments, lotions or foams) available.<sup>78</sup> The choice of the TCS depends on the patient's age, disease severity and location of AD lesions. Super-potent TCS (group IV) are not generally recommended for AD treatment, especially not in children. For routine treatment of flares, once-daily application of a potent TCS is sufficient, usually for 3–5 days. TCS should be started as soon as the first signs of the flare appear. Itch is a key symptom for evaluation of response to treatment, and tapering should not be initiated before itch has disappeared.<sup>1</sup> With mild disease activity, monthly amounts in the mean range of 15 g in infants, 30 g in children and up to 60–90 g in adolescents and adults, associated with a liberal use of emollients, generally allow a good maintenance with SCORAD values below 15–20.<sup>2</sup>

Topical corticosteroids should not be applied to the face every day for more than one month, because it may induce skin barrier fragility and rosacea-like perioral dermatitis. Intermittent use will reduce the risk of side-effects. Applying TCS on the inside of the thighs, upper arms and breasts (in females) for longer periods may cause stretch marks, particularly in adolescents. The risk of ocular complications with TCS seems to be low. Potent and very potent TCS (groups III and IV) are more likely to cause transient depression of adrenal function than group I (mild) and group II (moderate strength) treatments.<sup>79</sup>

The most constructive way to use TCS and avoid steroid-related side-effects is not to spare them during acute flares, but through early TCS intervention combined with consequent baseline emollient skincare to stabilize the disease.<sup>80</sup> Later on, proactive therapy should be used in the long term (see proactive therapy chapter below). The consequences of under treatment might be more serious than those associated with TCS

treatment.<sup>81</sup> The risk of inducing systemic side-effects is lower with the use of the relatively new topical steroids with short half-life, such as prednicarbate, fluticasone and mometasone. A short-course, well-conducted systemic treatment may be safer and more advisable than prolonged use of high potency TCS for AD. Trials for TCS treatment in children less than 2 years old are lacking as well as for long-term use of mid and high potency TCS in paediatric populations.<sup>81,82</sup> In practice, TCS are often used in combination therapies (emollients, TCI, topical antibiotics, cyclosporine A<sup>83</sup> or dupilumab<sup>84</sup>). Patients' and healthcare professionals' fear of side-effects of corticosteroids (corticophobia) is quite common and should be addressed.<sup>85</sup> The education of patients and healthcare professionals is required to increase adherence to treatments.<sup>21</sup>

The ETFAD recommends using TCS according to standard guidelines in combination with many other treatment modalities including patient education.

### Topical calcineurin inhibitors

TCI show quite good anti-inflammatory and very good antipruritic effects, whilst lacking adverse effects associated with TCS such as skin atrophy. TCI are especially useful in sensitive skin areas and occlusive areas, and in patients who need long-term treatment.<sup>78</sup> Two TCI, tacrolimus ointment and pimecrolimus cream, are licensed for topical AD treatment. The anti-inflammatory effects result from an inhibition of proinflammatory cytokine production by T cells and mast cells, whereas part of their antipruritic effects are attributed to a specific effect on TRPV1 neurons in the skin.<sup>86</sup> Applying the treatment twice a day is more effective than just once for the treatment of flares.<sup>87–90</sup> The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a TCS with intermediate activity,<sup>91</sup> while the latter is clearly more active than 1.0% pimecrolimus cream.<sup>92</sup>

Both TCI are safe to use and licensed for children aged 2 and above, and for adults.<sup>93,94</sup> Even long-term safety data from a 4- and 10-year tacrolimus and a 5-year pimecrolimus study exists.<sup>95,96</sup> Off-label use in children below 2 years of age is very common.<sup>94</sup> The most frequently observed side-effect is a transient warmth sensation or transient burning at the application site during the first days of application.<sup>87,92</sup> It starts about 5 min after each TCI application and may last up to one hour, but intensity and duration typically decrease with twice daily application within one week to zero.<sup>97</sup> A few days of initial treatment with TCS before switching to TCI may reduce the burning sensation, and an overlap period of one week may be advisable. A transient flush sensation following alcohol uptake is observed in few TCI-treated patients, which can effectively be blocked by taking 500 mg acetylsalicylic acid about 30 min before alcohol consumption. Patient education on these potential side-effects is required for adherence.<sup>21</sup>

Viral skin infections such as eczema herpeticum or eczema molluscum have been observed during TCI treatment.<sup>98,99</sup> In

patients experiencing recurrent eczema herpeticum, continuous prophylactic treatment with oral valaciclovir may be advisable.<sup>100</sup> None of the TCI induces skin atrophy.<sup>101,102</sup> This favours their use over TCS in delicate body areas such as the eyelid region, the perioral skin, the genital area, the axilla region or the inguinal fold and for topical long-term management. Clinical data do not indicate an increased risk of the induction of lymphoma or other types of malignancies,<sup>94,103</sup> or photocarcinogenicity,<sup>95,104,105</sup> for TCI, but UV protection, e.g. with sunscreens, is recommended for theoretical safety reasons.<sup>93,94</sup>

The ETFAD recommends first-line use of TCI in delicate body areas, with preference for pimecrolimus in mild AD, and for tacrolimus in moderate and severe AD and for long-term topical treatment. Off-label use below the age of 2 years is also recommended.

#### **Tar derivatives – aryl hydrocarbon receptor agonists**

Topical application of coal tar is one of the oldest therapies for AD, with long-standing but constantly declining clinical use and moderate efficacy.<sup>3</sup> Coal tar may restore filaggrin expression and counteract the Th2-mediated downregulation of skin barrier proteins by aryl hydrocarbon receptor (AHR) activation and STAT6 dephosphorylation, thus diminishing spongiosis, apoptosis and CCL26 expression in AD lesions.<sup>106</sup> The cosmetic acceptance of tar preparations is poor, but tar preparations may be considered in selected cases, for example those with lichenification. The use in infants is controversial.

Recently, a 12-week, double-blind, vehicle-controlled, randomized study was performed using various concentrations of tapinarof (GSK2894512; 5-[(E)-2-phenylethenyl]-2-(propan-2-yl) benzene-1,3-diol), an AhR-modulating agent in adult patients with AD (BSA 5%–35%).<sup>107</sup> The most effective treatment was the 1% formulation applied twice a day, with a statistically significant treatment success. The most frequent treatment-emergent adverse events were folliculitis and contact dermatitis. Tapinarof is currently not licensed in any country for AD or any other indication.

#### **Topical phosphodiesterase 4 inhibitors**

Phosphodiesterase 4 (PDE4) is a key regulator of inflammatory cytokine production in AD through the degradation of cyclic adenosine monophosphate.<sup>108</sup> A recent meta-analysis including 7 double-blind randomized clinical trials of topical PDE4 inhibitors vs vehicle treatment for 1869 patients with mild-to-moderate atopic dermatitis concluded that topical PDE4 inhibitors were effective and safe for patients with mild-to-moderate AD.<sup>109</sup>

The most extensively studied topical PDE4 inhibitor, crisaborole, was studied in two identically designed, vehicle-controlled, double-blind studies (28 days) in patients aged 2 years and older with mild or moderate AD. Despite a strong vehicle effect, more crisaborole-treated than vehicle-treated patients

achieved an Investigator's Static Global Assessment (ISGA) score of clear or almost clear with  $\geq 2$ -grade improvement.<sup>110</sup> Crisaborole ointment had a low frequency of treatment-related adverse effects over 48 weeks of treatment of patients with AD observed in a long-term safety study.<sup>111</sup> Clinical trials with crisaborole in very young children (3–24 months) and studies comparing the efficacy of crisaborole to TCS and TCI are running, but the results are not published. Crisaborole is licensed in the United States, but not marketed in the EU.

At present, no recommendation can be given regarding topical PDE4 inhibitors.

#### **Proactive therapy**

By tradition, topical anti-inflammatory therapy has been applied to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This reactive approach has been complemented by the proactive treatment concept, which is defined as a long-term, low-dose, anti-inflammatory treatment applied to previously affected areas of skin, in combination with use of emollients on the entire body and an appointment schedule for clinical control examinations.<sup>23</sup> Proactive therapy will prolong the time to relapse.<sup>32</sup> The proactive, usually twice-weekly topical treatment of previously affected areas is started only after all visible lesions have successfully been treated, in addition to daily ongoing emollient therapy for both previously affected skin and unaffected skin.<sup>32</sup> Clinical trial data are available for the TCS methylprednisolone aceponate and fluticasone propionate for up to 3 months, and for tacrolimus ointment for up to 1 year.<sup>112–115</sup> As a rule, barrier disruption is lower with proactive therapy than with daily application, as it is lower with TCI than with TCS.<sup>116</sup> Both TCS and TCI showed an antipruritic effect, with TCI being superior to TCS.<sup>117</sup> The cost-effectiveness of proactive therapy with topical tacrolimus has been demonstrated, as well as a beneficial effect on quality of life and lower aeroallergen-specific IgE levels in patients using proactive therapy.<sup>118,119</sup> Clinical experience and indirect evidence from many trials suggest that tacrolimus ointment, as well as TCS of Niedner classes II and III, are good candidates for proactive treatment, whereas pimecrolimus cream and TCS of Niedner class I are less efficient.<sup>32</sup>

The ETFAD recommends the introduction of proactive therapy with TCI or TCS in patients with moderate-to-severe AD.

#### **Phototherapy**

Phototherapy is a topical treatment option to improve skin lesions, pruritus and sleeplessness in AD patients, with remission periods up to 6 months and no documented serious short-term side-effects.<sup>120</sup> In AD, phototherapy affects several factors such as the suppression of the antigen-presenting function of Langerhans' cells, induction of antimicrobial peptides, the induction of apoptosis of infiltrating T cells<sup>121</sup>, a reduction in the colonization by *S. aureus* and *Malassezia* species<sup>122</sup> and a reduced antigen

presentation following an increased phototherapy-induced thickness of the stratum corneum.<sup>123</sup>

Phototherapy is frequently used for the treatment of AD, especially for the treatment of the chronic phase in adults.<sup>120</sup> Phototherapy is usually part of a complex treatment plan, i.e. a second-level treatment.<sup>3</sup>

UV treatments should not be used to treat acute, in particular oozing, lesions as this will often result in a worse outcome. Patients with acute flares should instead be treated with a standard regimen for some days before starting UV treatment.<sup>3</sup> Due to practical challenges, theoretical concerns and limited data on the use of phototherapy in children with AD, phototherapy is usually not considered in prepubertal children, although not contraindicated.<sup>3,4</sup> In practice, the limitations are the availability of UV light machines, feasibility and lack of efficacy on lesions on scalp and folds. Combined use of TCI with UV is still controversial, even if the initial warnings of an increased skin cancer risk have not been substantiated.<sup>105,124</sup>

Beside natural sunlight (NSL), phototherapy for AD may be useful with different artificial light sources: broad-spectrum UVB (280–315 nm), narrowband (nb-) UVB (311–313 nm), broadband UVA (UVA) (315–400 nm), UVA1 (340–400 nm), UVA1 cold light (with seawater baths) plus UVB (balneophototherapy) and psoralen plus UVA (PUFVA). UVA1 phototherapy can be applied as moderate-dose (MD) (50 J/cm<sup>2</sup>) and low-dose (LD) (10 J/cm<sup>2</sup>) regimen, whereas high dose (HD) (130 J/cm<sup>2</sup>) is not recommended anymore for AD treatment. Using 308-nm monochromatic excimer light allows the treatment of only limited areas.<sup>125</sup> Though blue light has been used for AD in an uncontrolled trial,<sup>126</sup> treatment with longer wavelengths has not been carefully studied for AD and is therefore not recommended.

nb-UVB is indicated for chronic moderate forms of AD and seems to cause less erythema compared with broadband UV. Medium-dose UVA1 appears to be similarly effective as nb-UVB,<sup>127</sup> but is more time-consuming. Concomitant treatment with TCS, emollients and phototherapy should be considered in order to reduce flare-ups.

UV light can also be combined with a prior (oral or topical) administration of photosensitizing drugs (psoralens): the so-called PUVA (photochemotherapy). All UV treatments and, even more, photochemotherapy pose a long-term risk of development of skin cancer, together with the proven prematurely ageing of the skin.<sup>120</sup> There are some data that individuals with filaggrin deficiency are particular at risk.<sup>128,129</sup>

Photochemotherapy for AD treatment has largely been abandoned due to its proven carcinogenicity and the fact that most AD patients are young.<sup>3</sup> Oral PUVA has a number of side-effects, which may include nausea, headache, fatigue, burning skin, itching and irregular skin pigmentation as well as an increased risk of skin cancer,<sup>120</sup> so the risk/benefit ratio of full-body treatment is usually unfavourable. In contrast,

the risk/benefit ratio of topical PUVA for palms and soles is usually favourable.

The ETFAD recommends concomitant nb-UVB or medium-dose UVA in combination with TCS or selected systemic therapy for the treatment of AD.

### Allergen Immunotherapy in AD

The efficacy and safety of allergen immunotherapy (AIT) in AD have been demonstrated in case reports, smaller cohort studies and a few larger multicentre trials. It is evident that AIT may improve the course of AD in selected patients rather than being a general risk of deterioration of the disease as anticipated by some patients and researchers.<sup>130</sup> Favourable effects of AIT on disease symptoms of AD appear to be higher if accompanying relevant type I sensitizations are present, but only house dust mite-sensitized patients have been studied in larger studies.<sup>131,132</sup> Here, the data for subcutaneous immunotherapy are stronger when compared to sublingual therapy and patients with severe AD (SCORAD > 50) showed better results.<sup>132</sup>

Patients with a positive APT, a positive challenge reaction or a history of eczema flares during the corresponding season, may be preferred candidates for future studies on AIT with the eliciting allergen. Regarding routine care, AIT is currently not recommended as a general treatment option for AD, but may be considered for selected patients with house dust mite, birch or grass pollen sensitization and severe AD.<sup>5</sup> Importantly, AIT may well be used in AD when approved indications for this treatment (allergic rhinoconjunctivitis or allergic asthma) exist in the same patient.

The ETFAD does not recommend AIT as a general treatment option for AD. However, AIT may be considered for selected patients with house dust mite, birch or grass pollen sensitization, who have severe AD and a history of clinical exacerbation after exposure to the causative allergen or a positive corresponding atopy patch test.

### Antihistamines

Systemic antihistamines targeting the histamine 1 receptor (H1R) are often used to reduce itch in acute AD flares, whereas topical application has only been studied for doxepin in AD. A few randomized controlled trials have been conducted which have shown only a weak or no effect in decreasing pruritus in AD.

Low-quality evidence indicated that H1R antagonists (H1RA) might be effective as 'add-on' therapy when compared to placebo.<sup>133</sup> Due to this analysis, fexofenadine may lead to a small improvement in patient-assessed pruritus, with probably no clinically relevant difference in the amount of treatment used to prevent eczema flares. Cetirizine and loratadine were not superior to placebo in terms of clinical signs or symptoms. Of note, in a frequently cited controlled study, cetirizine has not shown any effects on AD scores but a protective or inhibiting effect on

associated urticaria in AD patients.<sup>134</sup> Antihistamines are generally safe in use and may be tried to decrease pruritus and permit sleep during flares, but particularly the first generation of antihistamines may affect sleep quality. Therefore, long-term use of sedative antihistamines is not recommended. In fact, a recent retrospective study attributed a higher rate of attention-deficit/hyperactivity symptoms (ADHS) in children with AD and a history of medication with antihistamines.<sup>135</sup> Ongoing studies focus on the blockade of alternative histamine receptors such as H4RA, which may be more important in AD.<sup>136,137</sup>

In conclusion, there is not enough randomized control trial evidence to demonstrate the efficacy of topical antihistamines, including doxepin in the treatment of itch in AD.

The ETFAD does not recommend the general use of first- or second-generation H1RA for the treatment of pruritus in AD. H1RA may be tried for the treatment of pruritus in AD patients, if standard treatment with TCS, TCI and emollients is not sufficient. Long-term use of sedative H1RA in childhood is not recommended.

### Systemic anti-inflammatory therapy

Systemic therapy is necessary if AD cannot be controlled sufficiently with appropriate topical treatments and UV light therapy. It can also be useful to reduce the total amount of TCS in patients who need large amounts of potent TCS for vast body areas over prolonged periods to control their AD.<sup>138</sup> Before starting a systemic treatment, it is important to rule out differential diagnoses such as cutaneous T-cell lymphoma, potential trigger factors such as allergic contact dermatitis and behavioural and educational reasons for poor responses.<sup>74,139</sup> Until recently, rather broad-acting immunosuppressants, such as systemic corticosteroids (SCS), cyclosporine A (CyA), azathioprine (AZA), mycophenolate mofetil (MMF), enteric-coated mycophenolate sodium (EC-MPS) and methotrexate (MTX), were the only systemic treatment options for difficult-to-treat AD.<sup>140</sup> These systemic immunosuppressants can roughly be divided into two groups: SCS and CyA have a rapid onset of action and can be used to treat flares of AD or to bridge the time until onset of action of slow-acting systemic immunosuppressants such as MTX, AZA and MMF/EC-MPS. Dupilumab is the first biologic specifically licensed for AD, and many other biologics and small molecules are in advanced stages of clinical development.<sup>141</sup> The following recommendations for systemic drugs are based on expert opinions and medical considerations and may differ from the legal licensing status and access routes, which are not uniform in European countries.

### Systemic corticosteroids

Systemic corticosteroids (SCS) are rapidly effective, but have a largely unfavourable risk/benefit ratio.<sup>3</sup> SCS should only be used for 1–2 weeks for severe acute exacerbations due to the many long-term side-effects. A typical regimen for severe acute

exacerbations would be methylprednisolone maximal 0.5 mg/kg/day for 1–2 weeks and tapering over 1 month.<sup>3</sup> Short courses of SCS without adequate tapering can lead to high rates of relapse or rebound of the disease. In severe chronic cases, starting another oral immunosuppressive therapy while tapering the SCS should be considered. SCS must not be used for long periods of time due to significant risk of severe side-effects.<sup>3</sup>

### Cyclosporine A

Cyclosporine A (CyA) is frequently used and very effective for AD in both children and adults.<sup>142</sup> It is used at 3–5 mg/kg/day, divided into a morning dose and an evening dose. The dosage should be started at 5 mg/kg/day and can usually be tapered after 4–6 weeks to 2.5–3 mg/kg in the maintenance phase. CyA has a narrow therapeutic index and requires close monitoring of blood pressure and signs of renal impairment, especially in elderly patients. CyA is approved for systemic treatment of AD in adults in most European countries.<sup>142</sup> CyA may be used off-label for children or pregnant females.<sup>6</sup> Treatment duration usually varies from 3 months to 1 year, but some patients tolerate much longer low-dose CyA treatment very well.<sup>143</sup> CyA is usually considered as the first-line option for patients requiring immunosuppressive treatment,<sup>142</sup> although the drug survival for CyA is much shorter than for MTX.<sup>143</sup>

### Methotrexate

Methotrexate (MTX) has a slow onset of action. The recommended therapeutic doses are between 10 and 25 mg once weekly in adults and between 0.2 and 0.5 mg/kg/week in children (maximum dose 25 mg/week).<sup>3</sup> MTX is about equally effective as AZA and CsA in adults and children. The maximal clinical efficacy of MTX is reached after 8–12 weeks. Some reports suggest that in adult patients, higher dose of MTX (between 15 and 25 mg/week) could be used to reach maximum efficacy. Moreover, MTX showed good long-term effectiveness just like AZA. MTX is often well-tolerated and available for oral and subcutaneous administration. Infections, gastrointestinal disturbances and, in rare cases, myelotoxicity may limit the use of MTX. Each MTX cycle should be followed by a folic acid substitution.<sup>144–147</sup> MTX is hepatotoxic and teratogenic, and women of childbearing potential must use effective contraception during therapy.<sup>6</sup>

### Azathioprine

Azathioprine (AZA) has a slow onset of action, as the maximal clinical efficacy is reached after 8–12 weeks. A starting dose of 50 mg/day for 1–2 weeks is recommended in adults. Depending on acute adverse events such as gastrointestinal side-effects, liver enzyme elevation or haematological abnormalities, the dose can usually be increased to 2–3 mg/kg/day. Low thiopurine methyltransferase (TPMT) activity is associated with an increased myelotoxicity of AZA, but TPMT activity screening tests can

identify patients at risk before starting the treatment. If this test is not available, treatment can be started with half the dosage, whilst monitoring for side-effects. Although most clinical trials are of short duration, there is evidence that AZA is effective and safe for the treatment of AD for up to 5 years. However, drug survival is mainly limited due to side-effects.<sup>145,148</sup> AZA increased the risk of non-melanoma skin cancer and lymphoma in inflammatory bowel disease patients.<sup>95,104,149,150</sup> AZA may be used in children. In pregnant females, AZA should only be used on strict indication.<sup>6,151,152</sup>

### **Mycophenolate mofetil**

Mycophenolate mofetil (MMF) has a slow onset of action. A dose of MMF at 2 g/day and EC-MPS at 1440 mg/day is commonly used. However, enteric-coated mycophenolate sodium (EC-MPS) is equally effective as CyA as maintenance treatment in patients with AD. MMF may be used in children,<sup>5,152</sup> and the recommended dose is between 20 and 50 mg/kg/day. Mild gastrointestinal side-effects and haematological abnormalities are frequently observed during MMF treatment, but the general security profile seems to be quite favourable, making it an unlicensed but clinically useful treatment alternative for severe AD patients, especially for maintenance therapy. MMF and EC-MPS are both teratogenic, and women of childbearing potential must use effective contraception during therapy.<sup>6,148,152–154</sup>

The ETFAD recommends an initiation of classical immunosuppressive therapy with CyA, MTX, MMF or AZA only if topical treatment is not an option. The treating physician should have experience with these substances, and the choice of drug should consider all relevant patient- and drug-related factors including the patient's comorbidity, expected onset of efficacy, planned duration of treatment and licensing status of the drug.

### **JAK Inhibitors in clinical trials**

Janus kinase (JAK) inhibitors are fast-acting drugs, which suppress a wide range of pathways. There are multiple lines of evidence that the JAK-STAT signalling pathway plays a major role in AD. An advantage of inhibiting JAK1 is that it covers multiple cytokines involved in the pathophysiology of AD, including IL-4, IL-13, IL-31, TSLP and IL-22. A JAK1 inhibitor may therefore be effective where a more selective biologic such as Th2 blockers has been insufficiently effective, but more side-effects might be observed. Several oral JAK inhibitors are currently under investigation for the management of AD. More study data have been presented at congresses than have appeared in full publications in peer-reviewed journals. Some JAK inhibitors are already licensed for rheumatoid arthritis.

Baricitinib is an oral selective JAK1 and JAK2 inhibitor licensed for rheumatoid arthritis in many European countries. The results of three phase 3 studies investigating oral baricitinib at 1, 2 and 4 mg daily for the treatment of AD are published.<sup>155</sup> Two placebo-controlled monotherapy studies were conducted

without the addition of TCS (except as rescue therapy). 36% of patients achieved EASI 75 with baricitinib 4mg daily at week 16 without censoring for TCS rescue. In the third study, 47.7% of patients achieved EASI 75 when baricitinib 4mg daily was added to standard care TCS at week 16.<sup>155</sup> The most frequent adverse events were upper respiratory tract infections, headaches and an increase in blood creatine kinase.

Upadacitinib (ABT-494), an oral selective JAK1 inhibitor, showed reduction in pruritus as early as week 1 and improvement of the extent and severity of skin lesions as early as week 2 in a phase 2b trial.<sup>156</sup> At week 16, 69% and 50% of the patients achieved EASI 75 and EASI 90, respectively, with 30 mg daily. The most common relevant adverse events were upper respiratory tract infections and acne.<sup>156</sup>

Abrocitinib (PF-0496582) is another oral selective JAK1 inhibitor, which showed positive results in a phase 2b study.<sup>156</sup> Reduction in the EASI score was 82.6% for patients receiving 200 mg daily. 65% and 52% of the patients achieved EASI 75 and EASI 90, respectively, with 200 mg daily.<sup>157</sup> The most frequently reported, relevant adverse events were upper respiratory tract infections. Dose-dependent decreases in platelet count were observed but would recover back towards baseline levels after week 4.

JAK inhibitors are promising, fast-acting and potent therapies for the treatment of adult and adolescent AD. Dose selection for chronic treatment and long-term safety profiles will be important to assess, considering the potential risk of malignancies, serious infections and venous thrombosis. The more selective JAK1 inhibitors targeting only JAK1 may have less unwanted drug effects than the less specific JAK inhibitors.

The ETFAD recommends checking on a regular basis all upcoming information on JAK inhibitors, as the licensing of new drugs for the treatment of AD is likely.

### **Alitretinoin**

Alitretinoin offers anti-inflammatory and anti-proliferative effects. One large trial involving 1032 chronic hand eczema patients,<sup>158</sup> about one-third of which are probably atopic hand eczema patients, as well as a small case series of six AD patients<sup>159</sup>, indicate that this teratogenic drug is effective in atopic hand eczema and that bystander improvement of extrapalmal AD lesions is likely. Alitretinoin may be considered in adult atopic hand eczema patients unresponsive to TCS,<sup>3</sup> but is strictly contraindicated in pregnant women.<sup>6</sup>

### **Maternal and paternal exposure to oral immunosuppressive drugs**

The maternal benefit of oral immunosuppressive drugs in expecting AD patients must always be weighed on an individual basis against possible adverse effects such as spontaneous abortion, prematurity, low birthweight, adrenal insufficiency, infections and teratogenicity.<sup>6</sup> Treatment with CyA and SCS is well

possible during pregnancy, but the unfavourable risk/benefit ratio of SCS remains.<sup>3</sup> MTX, alitretinoin, MMF and EC-MPS are strictly contraindicated in pregnancy. Continuation of AZA treatment (halved dose) is considered possible on strict indication.<sup>6</sup>

Detailed ETFAD recommendations for the treatment of AD in pregnant women have been published in 2019.<sup>6</sup>

The relationship of paternal use of oral immunosuppressive drugs before fathering and congenital abnormalities is less clear than the effects of maternal use. Although studies are often small and of poor quality, several guidelines recommend for men using AZA or MPA to adequately use contraceptive measures during treatment and for three months thereafter.<sup>160</sup> It is recommended to wait three months after stopping MTX before fathering.

### Biologics

Although AD is considered to involve multiple immune pathways potentially underlying different disease subtypes, a strong activation of type 2 immune responses, driven by innate type 2 lymphoid cells and type 2 T-helper cells with their signature cytokines IL-4, IL-5 and IL-13, appears to be a dominant mechanism.<sup>141</sup> Targeting type 2 pathways is therefore a reasonable therapeutic strategy.

### Dupilumab

Dupilumab is the first biologic that has been approved as first-line treatment for moderate-to-severe AD in patients 12 years and older in the United States and in Europe. It is a fully human monoclonal antibody against IL-4R $\alpha$  that blocks both IL-4 and IL-13 signalling. In randomized controlled trials of up to 52 weeks, treatment with dupilumab as monotherapy or in combination with TCS improved multiple measures of AD signs and symptoms as well as health-related quality of life.<sup>161–165</sup> Data from registries and real-world case series showed comparable response rates.<sup>166–168</sup>

The safety profile of dupilumab is favourable with conjunctivitis and blepharitis being the most frequent side-effect observed in up to 22.1% of dupilumab users in clinical trials<sup>169</sup> and up to 38.2% in real-world settings.<sup>167</sup> Most conjunctivitis cases are transitory and can be successfully managed without dupilumab withdrawal.<sup>169</sup> Treatment options for dupilumab-associated conjunctivitis include artificial tears for mild cases, topical corticosteroid fluorometholone 0.1% eye drops, topical calcineurin inhibitor ointment applied to the eye lids for moderate, and eye drops or ointments containing cyclosporine or tacrolimus for severe forms.<sup>170–172</sup> In addition, a paradoxical head and neck erythema, also known as red face syndrome, may develop with prolonged use of dupilumab, but can be treated with topical antimycotic or anti-inflammatory preparations.<sup>173,174</sup> Noteworthy and in contrast to many other biologics, there appears to be no need for laboratory monitoring.<sup>175</sup>

Dupilumab should be combined with daily emollients and may be combined with topical anti-inflammatory drugs as needed.<sup>84</sup> Conventional systemic immunosuppressants may be continued in the first weeks after initiation of dupilumab treatment until the full clinical outcome is reached.<sup>166</sup> Dupilumab is currently approved for adults and children aged 12 years and above. Phase III data on children aged 6 years and above are available, and a timely approval for this age group is expected. The approval of dupilumab for certain forms of severe asthma and severe chronic rhinosinusitis with nasal polyposis by the EMA may also be relevant when choosing a drug.

The ETFAD recommends dupilumab for the treatment of patients aged 12 years or over with moderate-to-severe atopic dermatitis, who are candidates for systemic therapy.

### Biologics in clinical trials

Many other biologics, which interfere with different cytokines and signalling pathways, are currently being tested in phase 2 and phase 3 trials, e.g. tralokinumab (anti-IL-13), fezakinumab (anti-IL-22), etokimab (anti-IL-33), nemolizumab (anti-IL-31R $\alpha$ ) and tezepelumab (anti-TSLP),<sup>141</sup> and may become available in the next years.

Recently published phase 2 studies demonstrated that monoclonal antibodies blocking IL-13 (lebrikizumab, tralokinumab) are effective in patients with moderate-to-severe AD.<sup>176,177</sup> By applying fezakinumab, an anti-IL-22 antibody, a significant decline of disease severity scores (SCORAD, affected body surface area and investigator global assessment) could be achieved and a pathogenic role for IL-22 in severe AD was demonstrated.<sup>178</sup> Two-phase 2 studies with nemolizumab, the anti-IL-31 receptor antibody, showed a large reduction in pruritus and in parallel improvement of clinical signs of AD underlining the role of the itch-scratch cycle.<sup>179,180</sup> The improvement of pruritus and dermatitis scores from baseline is maintained or may even increase upon long-term treatment (up to 64 weeks) with nemolizumab.<sup>181</sup> The difficult-to-treat subgroup of patients with prurigoform AD may profit especially well from nemolizumab.<sup>182</sup> A proof-of-concept study reported a rapid and sustained effect of a single administration of etokimab, an anti-IL-33 monoclonal antibody, in patients with AD.<sup>183</sup>

The ETFAD recommends checking on a regular basis all upcoming information in this field, as the licensing of new drugs for the treatment of AD is likely.

### Antibacterial and antimycotic therapy

AD patients are more susceptible to secondary skin infections which tend to generalize, especially with *S. aureus*, *Malassezia furfur* and herpes simplex virus.<sup>184,185</sup> The inflammatory micro-milieu initiated by thymic stromal lymphopoietin (TSLP), IL-4 and IL-13 downregulates important cutaneous antimicrobial peptides such as cathelicidin LL-37, dermcidin and human  $\beta$ -defensins HBD-1, HBD-2 and HBD-3.<sup>184,186</sup> The understanding of colonization and

infection in AD has largely increased by detailed investigation of the human microbiome. A *S. aureus*-driven loss of diversity of the cutaneous microbiome is significantly associated with flares of AD, but not if patients have followed a proactive therapy regimen before the flare.<sup>187</sup> In up to 90% of AD patients, even non-lesional skin is extensively colonized by *S. aureus*. Many commensal bacteria, such as *S. epidermidis*, produce inhibitors that decrease *S. aureus* growth.<sup>188</sup> Strains of *S. aureus* found on AD patient's skin are different from strains isolated from the nasal carriers in normal population.<sup>189</sup>

*S. aureus* is a major trigger of AD, as inflammation is triggered through the release of toxins with superantigenic properties. These superantigens enhance T-cell activation in the skin, and also increase the expression of IL-31, leading to pruritus.<sup>190</sup> Scratching favours binding of *S. aureus* to the skin, and the increased amount of *S. aureus*-derived ceramidase aggravates the skin barrier defect. Moreover, superantigen production increases the expression of alternative glucocorticoid receptors that do not bind topical corticosteroids, which leads to steroid resistance.<sup>191</sup> Biofilm formation by AD-associated staphylococci may play a major role in the occlusion of sweat ducts leading to inflammation and pruritus.<sup>192</sup>

### Antibacterial therapy

Regular cleansing of the skin with syndets, topical antiseptics and antibiotics, systemic antibiotics and functional textiles have been used to reduce *S. aureus* on AD patients' skin. In clinical practice, a selection must be done based on clinical aspects, as all of these measures have strengths and weaknesses. Most interventions aim at reducing the burden of *S. aureus*.

Newly developed emollients include active compounds that influence the microbiome of AD with bacterial lysates from *Aquaphilus dolomiae* or *Vitreoscilla filiformis* species.<sup>193</sup> These are usually well-tolerated and improve the epidermal barrier as an added value, but the antibacterial effect against *S. aureus* seems low compared with antiseptics or systemic antibiotics. Physicians should not forget that a proper, well-conducted anti-inflammatory therapy with TCI or TCS will also reduce the colonization with *S. aureus*.

Both topical antiseptics and topical antibiotics may reduce *S. aureus* and other potentially helpful bacteria from the skin, but bacterial resistance and contact allergy are an issue. There is no clear benefit of antiseptic bath additives, antiseptic soaps or other antimicrobial agents added to topical therapies in non-infected atopic dermatitis, as evidenced in a large systematic review of 26 studies including 1229 participants.<sup>194</sup> Nevertheless, if there is no response to topical TCS or TCI, or evident infection, the use of topical antiseptics may be considered. These are preferred over topical antibiotics, as the development of bacterial resistance is less likely. A more recent systematic review published in 2017 confirmed these results.<sup>195</sup>

Sodium hypochlorite 0.005% has antiseptic properties and enhances in addition epidermal thickness and proliferation.<sup>196</sup> Its intermittent use showed a significant decrease in AD severity.<sup>197</sup> The addition of 100 mL of normal sodium hypochlorite household bleach (most come as 5% solution) to a full bath of 100-L tap water is the usual procedure. Potassium permanganate, which is the classical antiseptic substance, may stain bathtubs and patients and is difficult to get in some countries.

Impetigo is easily diagnosed by the yellow crusts and can be treated with fusidic acid, topical mupirocin or topical retapamulin for 5 days.<sup>198</sup> The high rate of *S. aureus* resistance against fusidic acid in Europe compared with the United States reflects the more frequent use in Europe.<sup>199</sup>

Systemic antibiotics should only be used in case of apparent and extensive bacterial superinfection. Based on the current resistance spectra, cephalexin or another first-generation cephalosporin can be recommended.<sup>200</sup> Children with AD seem to have a much lower rate of community-acquired methicillin-resistant *S. aureus* infection compared with the general paediatric population.<sup>201</sup>

Hidden sources of bacteria are cream and ointment containers, of which up to 53% are contaminated by bacteria, in 25% by *S. aureus*. Thus, the following recommendations seem to be useful<sup>202</sup>: (i) keep open moisturizers in refrigerator; (ii) use pumps or pour bottles rather than jars; (iii) avoid direct contact with hands and decant; and (iv) avoid sharing personal hygiene items.

The ETFAD recommends considering topical antiseptic drugs and antiseptic baths in addition to an adequate anti-inflammatory treatment with TCS and TCI, if clinical signs of strong colonization or bacterial superinfection are present. A long-term application of topical antibiotics is not recommended due to the risk of increasing resistances and sensitizations. A short course of systemic antibiotics, such as a 1st-generation cephalosporin, may be considered in AD patients with widespread and severe *S. aureus* infection.

### Antimicrobial textiles

Various functional textiles with antimicrobial properties and different qualities have been on the market for years and have been worn for either 24 h or overnight only. Silver-coated textiles are assumed to release low amounts of silver ions to the skin, where a moderate antiseptic effect is observed. The physical stability and resistance to repeated washings of these different textiles are quite heterogeneous.<sup>203</sup> AEGIS-coated silk textiles are another product line in this niche.

Silver-impregnated textiles have shown significant antimicrobial activity, as well as improvement of localized SCORAD in an unblinded, side-to-side controlled clinical trial.<sup>204</sup> In patients with uninfected AD, the use of silver-impregnated textile compared with cotton underwear did not reduce AD severity.<sup>205–207</sup> However, some functional textiles (silver-coated, acid-coated and silk

textiles) as well as chitosan, a natural biopolymer with immunomodulatory and antimicrobial properties, may possibly improve AD manifestations, as they decrease skin colonization by *S. aureus* and reduce itch.<sup>208</sup> Some of these newer options are still under investigation regarding the safety of silver-coated textiles in infants and toddlers. AEGIS-coated silk textiles did not show clinical benefit in a well-controlled, multicentre clinical trial.<sup>209</sup>

More recent studies evaluated these antimicrobial textiles in real life. Some silver-impregnated textiles lose their antimicrobial activity after 70 laundry cycles, whereas some others remain intact and still effective after 150 laundry cycles.<sup>203</sup> A second study described that this kind of textiles was unable to modify skin colonization with *S. aureus* under practical wear conditions (dry textiles), but the effectiveness could be enhanced by wetting the textiles. The authors found also that some moisturizing cream remains on the fibres after laundry.<sup>210</sup> In conclusion, efficacy and stability have been demonstrated for some silver products, and all silk and silver products are considered safe.

The ETFAD recommends considering high-quality silver garments to AD patients tending to strong colonization or infection with *S. aureus*.

### Antiviral therapy

Viral infections with herpes simplex virus, varicella zoster virus, molluscum contagiosum virus, smallpox virus and Coxsackie virus occur more frequently in AD patients than in healthy individuals, with a tendency to cause disseminated, widespread disease.<sup>185</sup>

Eczema herpeticum (EH), a disseminated *herpes simplex virus* (HSV) infection, is a potentially lethal complication of AD that requires immediate medical action. Patients, mostly children, present with disseminated, distinctly monomorphic vesicles, fever and lymphadenopathy. Complications such as keratoconjunctivitis, meningitis and encephalitis are rarely encountered.<sup>100</sup> A depletion of plasmacytoid dendritic cells, a failure of upregulation of the antimicrobial peptide LL-37 and an unmasking of the entry receptor nectin-1 by lesional spongiosis are considered relevant for the pathogenesis of EH.<sup>100,211</sup> IL-4 and IL-13 suppress keratinocyte expression of the antimicrobial peptide LL-37, which has a potent antiviral activity against HSV.<sup>212</sup> Some genetic variants of transcription factor STAT6, which regulates IL-4, are associated with EH in AD patients.<sup>213</sup> Predisposing factors of EH are early onset of AD, severe or untreated forms of AD, filaggrin deficiency, high total serum IgE level, elevated allergen-specific IgE and peripheral eosinophilia.<sup>185,214</sup> Almost all EH patients are of the extrinsic AD subtype<sup>100</sup>, and Th2 polarization of HSV-1 specific T cells has been shown in EH patients.<sup>215</sup> Pretreatment with TCS does not seem to imply an increased risk of developing EH, whereas TCI may do so and should be paused for some weeks.<sup>216</sup> Mainstay of EH therapy is a systemic treatment with aciclovir or valaciclovir.<sup>213</sup> Treatment

should be started immediately once the diagnosis is clinically suspected.<sup>3</sup> Patients with AD have a fourfold increased risk of developing ocular HSV infections. For AD patients with a history of HSV keratitis, a long-term oral antiviral prophylaxis may be advisable because of the potential vision loss risk due to scarring cornea.<sup>217</sup> The rate of localized HSV infections in AD patients treated with dupilumab is higher compared with placebo, but lower for EH and varicellazoster virus infection.<sup>218</sup>

*Varicellazoster virus* (VZV) infection in an immunocompetent child is usually a mild, self-limited disease. This infection is known to facilitate secondary local or systemic bacterial infection, which is cause for particular concern in AD children. The safety and efficacy of VZV vaccination in AD children are well-established.<sup>219</sup> Moreover, in children with AD, common childhood immunization in the first year is not associated with an increased risk of more severe AD or allergic sensitization; also, immune response to VZV vaccine is comparable to healthy children.<sup>220</sup> Therefore, parents of atopic children should be encouraged to follow their local vaccination plan including VZV vaccination.

*Molluscum contagiosum virus* (MCV) infection is in general benign and self-limited, but dissemination is frequent in AD patients, and therefore, treatment is recommended. MCV infection seems to be a trigger for disease onset or flare of AD in children with a positive family history of AD.<sup>221</sup> A large variety of topical treatments have been reported such as cantharidin, potassium hydroxide, tretinoin cream, topical cidofovir and others.<sup>222</sup> Physical therapies including cryotherapy and curettage are also effective, but not always well-tolerated in paediatric patients.<sup>185</sup> Topical treatment of AD with TCS and TCI may be continued during MCV infection.

*Eczema vaccinatum* (EV) is a complication of smallpox vaccination known to occur in AD patients. The vaccinia virus disseminates and causes an extensive rash and severe systemic illness with a mortality rate estimate at 5%–40%.<sup>223</sup> Therefore, smallpox vaccination is contraindicated in patients with a history of or currently active AD.<sup>224</sup> The existence of an attenuated vaccine and three antiviral drugs, in addition to vaccinia immunoglobulin, provides means of preventing or treating EV.<sup>225,226</sup> Should a smallpox outbreak necessitate an emergency mass vaccination, the choice of vaccination strategies has to be determined by policymakers.

*Eczema coxsackium* (EC) is a disseminated form of Coxsackievirus infection mostly occurring in children with active AD lesions. The Coxsackievirus A6 strain leads to atypical disease manifestations, which are classified as diffuse form (lesions extended to the trunk), acral form (lesions with a mainly acral distribution) or eczema coxsackium (disseminated lesions on pre-existing eczematous areas).<sup>227</sup> Symptomatic treatment includes use of TCS and wet-wrap therapy.<sup>228,229</sup>

The ETFAD recommends following all regional vaccination programmes including the VZV vaccination as recommended.

Parents of atopic children should be encouraged to fully immunize their children. The denial of vaccination because of diagnosed AD is a common misconception possibly leading to fatal consequences (see chapter: general measures). Eczema herpeticum should be treated upon suspicion immediately using systemic antiviral therapy, such as systemic acyclovir or valaciclovir.

### Antifungal therapy

*Malassezia spp.* is a commensal on healthy human skin, but is attributed a pathogenic role in AD, as it may interact with the local skin immune response and barrier function. There is evidence for a molecular mimicry between fungal and human superoxide dismutase and thioredoxin proteins, which may contribute to the pathogenesis of AD.<sup>230</sup>

Several randomized, placebo-controlled trials investigated the benefit of topical or systemic antifungal treatment for AD patients.<sup>231,232</sup> The ambiguous results of these clinical trials might be attributed to a selection bias. It can be speculated that antifungal therapies are more effective in certain subgroups of AD. It seems, for example, that antifungal therapy shows beneficial effects in patients with a head–neck-type distributed AD and detectable IgE-mediated sensitization against *Malassezia*.<sup>233</sup> Sensitization against this skin-colonizing yeast correlates with disease activity.<sup>234</sup> The most common class of antifungal drugs prescribed for AD patients are azoles such as ketoconazole and itraconazole, which have also some anti-inflammatory properties.<sup>232</sup>

The ETFAD recommends considering antifungal treatment with either topical ketoconazole or ciclopirox olamine for patients suffering from atopic head–neck dermatitis, and particularly for those with known IgE-sensitization to *Malassezia spp.*

### Complementary medicine for the treatment of AD

Complementary medicine describes a wide variety of healthcare practices used alongside standard medical treatment. Examples of complementary medicine include alternative health approaches such as traditional Chinese medicine, homeopathy and naturopathy.<sup>5</sup> Many patients with AD, in some studies over 50%, have used complementary medicine for primary or adjunctive treatment.<sup>235,236</sup>

There are an increasing number of trials studying complementary medicine for the treatment of adults and children with AD.<sup>237</sup> The most frequently used modalities are herbal medicine, vitamins, Ayurveda, naturopathy, homeopathy and traditional healing.<sup>237</sup> Most studies are small and with low methodologic quality.<sup>5</sup> Many studies do not report adverse effects in a proper way and safety often remains unclear due to insufficient reporting.<sup>237</sup> It should be noted that kidney failure and liver damage have been reported in association with traditional Chinese medicine.<sup>238</sup> A Cochrane review published in 2013 included 28 randomized controlled trials comparing Chinese herbal medicine (CHM) to

placebo. The authors could not find conclusive evidence that CHM taken orally or applied topically to the skin could reduce the severity of eczema in children or adults.<sup>239</sup> Another Cochrane review showed that oral borage oil and evening primrose oil lack effect in eczema.<sup>240</sup> The effect of n-3 (or omega 3) long-chain polyunsaturated fatty acid supplementation in pregnant or breastfeeding women on allergy outcomes in their children was assessed. For any allergy, no clear differences were seen in children between 12 and 36 months, nor beyond 36 months of age.<sup>241</sup>

No evidence-based recommendations can be made from the available literature.<sup>238</sup> There is a great need for higher-quality studies to guide patients as well as clinicians. Well-designed randomized trials are necessary to confirm a beneficial effect and to establish safe use. Future studies should be designed as double-blinded, placebo-controlled trials, with sufficient power and reported according to the CONSORT (Consolidated Standards for Reporting Trials) statement.<sup>242,243</sup> It is also important that the core outcome set and core outcome instruments are chosen in accordance with the harmonizing outcome measures for eczema.<sup>244,245</sup>

The ETFD does not recommend complementary medicine for the treatment of AD.

### Vitamins and probiotics

The role of vitamin D and the vitamin D receptor (VDR) in AD has been studied in three single centre randomized placebo-controlled studies including a total of 142 patients. One study found a significant clinical effect, but concomitant routine treatment was allowed and not registered.<sup>246</sup> Better-designed studies did not find a beneficial effect of vitamin D supplementation on AD manifestations.<sup>247–249</sup> A recent systematic review, focused on the effects of vitamin D levels and supplementation in children with AD, confirmed a link between serum vitamin D levels and AD severity, but only weak evidence was found supporting improvement of AD with vitamin D supplementation.<sup>250</sup> Hence, supplementation of vitamin D is useful neither for treatment nor for prevention of AD.<sup>251</sup>

Treatment regimens with probiotics aim to modulate the microflora in the gut in order to stimulate the immune response towards an allergy-protecting, T-helper 1-biased immune reaction.<sup>252</sup> There are several studies on the therapeutic effects of probiotics, but recent meta-analyses on the effect of probiotics in pregnant women<sup>253</sup> and in children<sup>254</sup> do not demonstrate convincing effects of this treatment modality compared with earlier meta-analyses.<sup>255,256</sup> In a recent Cochrane review assessing the effects of probiotics for treating patients of all ages, the authors concluded that compared to no probiotics, currently available probiotic strains probably make little or no difference in improving patient-rated eczema symptoms.<sup>257</sup>

The ETFAD does not recommend vitamin D or probiotics for the treatment of AD.

### Specific considerations for children

The anatomical and pathophysiological peculiarities of children, such as an incomplete skin barrier, a higher surface-to-body weight ratio, a less experienced immune system – together with the fact that many drugs effective for AD are not licensed for them – result in special considerations and treatment rules for young AD patients, especially for those aged 2 years and younger. The larger surface area-to-body weight ratio in infants can result in an up to 2.7 times higher systemic exposure which implies a greater risk of intoxication.

The clinical presentation of infantile AD shows different predilection sites and a tendency towards exudative lesions, especially on the cheeks. Establishing a diagnosis of AD may be difficult in this age group, because the classic diagnostic criteria cannot be applied. In early-onset severe AD (<3 months), some primary immunodeficiency syndromes such as Omen syndrome, selective IgA deficiency, hyper-IgE syndromes and Wiskott–Aldrich syndrome, some genetic disorders with an impaired barrier function such as Comel–Netherton syndrome and peeling skin syndrome, and some inherited metabolic diseases such as biotin deficiency or phenylketonuria may be differential diagnoses.<sup>258</sup>

Stress and conflicts in the family may trigger AD in young children. Flares are associated with contact to non-familiar pets, swimming in chlorinated pools and direct skin exposure to wool (except superfine merino wool<sup>259</sup>) and nylon textiles.<sup>260</sup> Prevention and early recognition of atopic respiratory diseases and food allergies are important during childhood and adolescence. In children, food allergies triggering an exacerbation are more common than in adults. For small children, cow's milk protein and hen egg are the most common relevant allergens. In adolescents, pollen-associated food allergens are more important. Food allergies in young children are often transient, making follow-up investigations necessary to assess the development of tolerance.<sup>261</sup> Attention-deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD) have been identified as possible comorbidities of AD.<sup>262</sup>

The principles of topical treatment are the same as in adults, but are adapted with respect to an increased absorption and altered surface-to-body weight ratio. The use of weaker TCS (classes 1 and 2) in small children is common practice of many dermatologists and paediatricians. Especially critical areas in infants are the diaper area, the face and the scalp. An increased use of TCI to spare TCS is widely advocated due to the ever-increasing experience and long-term safety data with the substance class.<sup>32,93</sup> The off-label use of both TCIs in children under 2 years of age has been considered appropriate in the latest European Guideline on Treatment of AD, based on good-quality long-term safety data recently published for TCI in infants.<sup>4,95,96</sup>

Hypoallergenic topical preparations should be prescribed in children with AD, as these have a significantly higher risk of developing contact allergy to components of skincare products

than children with healthy skin.<sup>263</sup> Glycerol as a moisturizer in emollients is better tolerated than urea in children under 5 years of age. Urea is a good emollient ingredient if used at 5% or less. It is not only a humectant, but also induces the expression of NMF ingredients in the skin. Sophisticated emollients may contain urea, glycerol and ceramides. There are good data from the AD flare prevention trials on tolerability. Topical drugs leading to severe side-effects include salicylic acid and disinfectants containing alcohol.<sup>264</sup>

Systemic treatment for children is administered on an individual patient basis in severe cases only, and there is no consented standard treatment for the substances or the duration. The most commonly used anti-inflammatory drug in Europe was CyA, followed by SCS and AZA.<sup>265</sup> Recently, low-dose MTX was shown to have a good safety profile in children,<sup>266,267</sup> even for long-term treatment,<sup>147</sup> and an effectiveness comparable to CyA.<sup>268</sup> Difficult-to-treat nummular forms of AD in children have also responded to MTX treatment.<sup>269</sup> Most systemic treatment of children and adolescents is expected to shift to dupilumab, once the expected licence for children is obtained.

Nocturnal pruritus is a common problem in medium-to-severe AD. A recent Cochrane Review concluded that there is no consistent evidence for the effectiveness of oral H1 antihistamines.<sup>133</sup> Sedating H1 antihistamines may be tried for a short period in acute exacerbations, when sleep disturbances persist despite TCS and emollient use,<sup>270</sup> but long-term use is not recommended.

Vaccinations, including those against measles, are generally safe in hen's egg-allergic AD patients,<sup>271</sup> the only restriction being the quality of skincare to avoid superinfection at injection sites. Though smallpox vaccination was contraindicated in children with AD to avoid eczema vaccinatum,<sup>224</sup> vaccinations against varicella are recommended to avoid severe cutaneous viral infections.<sup>4</sup>

Therapeutic parent and child education ('eczema school') is an integrated part of AD management and especially valuable for reducing AD symptoms.<sup>77,272</sup> Written treatment instructions, such as the 'Personalized Written Action Plan for Atopics', may be very useful.<sup>273</sup> For treatment adherence, it is important to establish a good relationship with the parents and consider the burden of disease they carry.<sup>21</sup>

The ETFAD recommends that for children, especially below 2 years of age, increased attention should be paid to the safety, tolerability and hypoallergenic properties of all components of topicals for the treatment and skincare of AD. Systemic treatment should be initiated by experienced specialists only.

### Specific considerations for adolescents

Adolescents are neither children nor adults, and to optimize the management of their AD, some specific elements should be considered. Adolescent patients develop more autonomy and must

learn to take care of their chronic disease in an independent way. Adolescent becoming the actors of their own skincare must be addressed directly and is possible without their parent's presence. Specific aspects have to be discussed such as sleep habits, daily skin treatment routine, management of comorbidities and aspects of health-related quality of life such as peer relationships, intimacy, sexuality and body image.<sup>274</sup>

Evaluation of daily skincare is essential. It seems that particularly adolescents either do not bath or shower much or do so with an excessive duration, which can aggravate AD and increases the risk of skin infection.<sup>36</sup> Adherence to a daily treatment routine is very difficult in this age group. The risk of striae from TCS absorption during puberty is high, and wet-wrapping therapy with TCS should be used as a short-term therapy and with caution only.<sup>275</sup> Therefore, adolescents need clear advice on how to use their TCS in combination with emollients<sup>276</sup> and specific age-related therapeutic patient educational programmes should be discussed as effective long-term management strategies of the disease.<sup>77</sup>

Teenagers with AD are more prone to specific types of allergic contact dermatitis.<sup>277</sup> The most frequent allergen is nickel. It could be present not only in belt buckles, button flies and jewelries, but also in cell phone covers and electronic devices.<sup>278</sup>

Adolescents with AD are more likely to experience psychological challenges compared with their healthy peers. Children of all age groups with AD had a significant increased risk of total mental disorders compared with those without AD.<sup>279</sup> Particularly in late adolescence, AD is associated with suicidal ideation and mental health problems.<sup>280</sup> Adolescents with AD have a higher risk of the developing a depressive or anxiety disorder later in life.<sup>281</sup> The relationship between suffering from AD and mental disorders may be reciprocal.<sup>282</sup>

Most adolescents with AD have experienced social exclusion or were bullied during childhood due to their skin disease, which negatively affects self-perception and self-esteem.<sup>283</sup> Older children or adolescents reportedly have fewer friends, participate in less social events or sports teams.<sup>284</sup> The way an adolescent feels about his body image is closely linked to self-esteem and difficulties related to body image are common in adolescence. Therefore, AD can also have a heavy impact on the capacity for intimacy and sexual life, as it implicates appearance and personal relationship. As quality of life correlates with the severity of AD and psychological or social impairment, a holistic approach could include psychological assessment, psychotherapy, behavioural therapy and coping strategies.<sup>285,286</sup>

AD can have an impact on school performance and on future professional life. Developing AD later during childhood or adolescence could lead to a higher risk of having persistent AD in adulthood, which can have an impact on the productivity at work.<sup>287</sup> However, having AD during adolescence does not seem to negatively impact academic performance.<sup>288</sup> Therefore, career choices should be discussed with adolescent patients.

The ETFAD acknowledges the special requirements of adolescent AD patients and recommends discussing them actively.

### Occupational aspects

AD patients are running a significant risk of developing occupational contact dermatitis. Atopy amplifies the effects of irritant and allergen exposure in hairdressers, cleaners, metalworkers, mechanics and nurses, where hand eczema is a very common disease.<sup>76</sup> The skin of patients with AD is more reactive to skin irritants, which in turn increases their risk of developing occupational irritant and allergic contact dermatitis on the hands.<sup>289</sup> Accordingly, patients with AD have three- to fourfold increased risk of occupational hand eczema.<sup>290</sup>

Occupations in which exposure to skin irritants such as water, detergent, machine oil and gloves is common can therefore be challenging for individuals with a history of AD. Physicians should inform their patients with AD about these risks and provide careful guidance about prophylactic skin protection. The risk of occupational hand eczema is generally higher for hairdressers, mechanics, bakers, chefs, nurses and painters. Adolescents with AD should consider this when choosing their profession.

The ETFAD recommends that preventive strategies should be developed and optimized to reduce the incidence of occupational dermatitis in AD patients. Dermatologists should advise their AD patients early on occupational aspects of their disease and suitable career choices.

### Psychosomatic aspects and therapeutic patient education

#### Psychosomatic aspects of AD

Psychosomatic treatment could complement topical and systemic therapy and should be divided into unimodal and multimodal psychological itch treatments.<sup>291</sup> Depending on the factors involved, a unimodal (e.g. progressive muscular relaxation or autogenic training)<sup>292</sup> or multimodal psychological approach is recommended.<sup>291</sup>

The vicious itch-scratch cycle has to be considered when a patient is treated for pruritus. The psychosomatic approach recognizes the itch patient with regard to coping behaviour and possible stress attempts as cause or provocation factor in chronic itch. Parents' behaviour and skincare management may influence the severity of the disease.<sup>293</sup> In addition to causal and symptomatic therapy, behavioural therapy to avoid scratching should be considered, e.g. conscious suppression of the reflex by intense concentration, distraction or alternative scratching techniques such as habit reversal.<sup>294</sup> This is very important in patients with AD and especially in those who might show an unconscious automatic scratching behaviour.

Adjuvant psychosocial programmes focused on itch are most effective in AD, and many randomized controlled trials have

been published in the recent years.<sup>295–306</sup> Such programmes include strategies for breaking the vicious circle of itching and scratching, relaxation and stress management techniques as well as strategies for dealing with relapses. More than 10 randomized controlled studies<sup>296,307,308</sup> and a Cochrane review about psychological interventions showed slightly beneficial effects.<sup>309</sup> Overall, counselling of AD patients is cost-effective.<sup>307,310</sup>

A similar educational programme was developed for patients with chronic pruritus.<sup>311,312</sup> It is currently established for in-patient hospital treatment of patients with pruritic dermatoses using behavioural therapy in the context of an integrated psychosomatic treatment.<sup>300,313</sup> Habit-reversal techniques are especially effective as an additional management for itch in AD patients.<sup>314</sup> Relaxation techniques are easy to practice and are demonstrated in specific age-related therapeutic patient educational programmes.<sup>22,77</sup> In patients with coexisting depression, psychotherapy in combination with psychotropic medication can be helpful even to treat pruritus of different aetiology.<sup>315</sup> Most publications on psychotherapeutic and psychopharmacologic interventions, however, refer to small groups or single case reports.<sup>316,317</sup> Internet-delivered (eHealth) self-management was investigated in recent years mostly with cognitive behavioural interventions.<sup>306,318</sup> Results demonstrate similar effects such as face-to-face psychotherapy.<sup>319</sup> Studies involving dermatologic patients are promising.<sup>320</sup>

The ETFAD recommends multimodal education programmes to increase coping behaviour in patients suffering from AD. Relaxation techniques and habit-reversal techniques for AD patients are also useful as a complementary treatment for managing the disease.

### Therapeutic patient education (eczema school)

Poor adherence to prescribed treatment is frequent and leads to therapeutic failure.<sup>21</sup> There is a significant and urgent need for physicians to ensure that patients with AD are educated and confident in using medication as prescribed to gain disease control. This education is designed to train patients or parents of children suffering from AD in the skills of self-management or adapting treatment to their particular chronic disease and in coping processes and skills. Educational intervention will help for the management of difficult-to-treat atopic patients. Standardized interdisciplinary programmes involving dermatologists, paediatricians, psychologists, psychosomatic counsellors and dietary counselling have been demonstrated to improve subjective and objective symptoms, optimize medication use in patients and result in a significant gain in quality of life.<sup>22,77</sup> Support materials for healthcare professionals and for parents can be found on >[www.fondation-dermatite-atopique.org](http://www.fondation-dermatite-atopique.org)<.

The ETFAD recommends participation in a therapeutic education programme for AD to all patients with moderate and severe AD.

### Optimizing patient adherence

Poor treatment adherence is one of the most common causes of treatment failure. Hence, the ability to distinguish reliably between non-adherence and non-response, and mastering the active use of adherence-improving strategies are most important for treating AD patients successfully.<sup>21</sup> Factors influencing treatment adherence include patient characteristics and beliefs, treatment efficacy and duration, administration routes and disease chronicity. Moreover, the quality of the physician–patient relationship including physician-time available for the patient as well as ‘shared decision-making’ plays an important role.<sup>21</sup> Strategies to increase treatment adherence range from handing out written action plans, minimizing treatment costs, thoughtfully scheduled follow-up visits and reminder programmes to simplifying prescriptions or educational interventions.<sup>21,273</sup> A recent systematic review summarizes the evidence and recommendations.<sup>21</sup>

### Outlook and future perspectives

The simultaneous emergence of many new topical and systemic drugs for the treatment of AD in clinical trials, and the perspective for some licensed systemic drugs even for childhood AD in the near future have considerably changed the field of AD management. A combination of limited resources and increased digitalization will emphasize the quality of care as an important issue also for the management of AD.<sup>321</sup> The impact of the COVID-19 pandemic on the availability of health care resources for AD patients cannot be predicted, even if an interaction with systemic medication seems low.<sup>322</sup> A carefully selected topical emollient therapy, allergen avoidance based on a thoroughly taken history and allergy testing, and a wise selection of topical anti-inflammatory therapy will still be needed in the future. Therapeutic patient education for children, their caregivers and adult patients suffering from AD supports and assures medical treatment, as it is safe and cost-effective. Moreover, digitalization of many aspects of patient care and artificial intelligence will for sure enter the field of AD management. Many new aspects of evidence-based care for AD patients will further change our daily practice in the next 5 years. New patient leaflets replacing the current ETFAD patient information sheet available at <<https://www.eadv.org/patient-corner/leaflets>>, and additional online information will witness these changes in due time.

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## Appendix 1

S. Barbarot, Nantes, France; T. Bieber, Bonn, Germany; P. Chernychov, Kiev, Ukraine; S. Christen-Zäch, Lausanne, Switzerland; M.J. Cork, Sheffield, United Kingdom; U. Darsow, Munich, Germany; M. Deleuran, Aarhus, Denmark; M. de Bruin-Weller, Utrecht, The Netherlands; L. De Rave, Brussels, Belgium; C. Flohr, London, United Kingdom; R. Fölster-Holst, Kiel, Germany; C. Gelmetti, Milan, Italy; U. Gieler, Gießen, Germany; A. Heratizadeh, Hannover, Germany; D.J. Hijnen, Rotterdam, The Netherlands; B. Kunz, Hamburg, Germany; C. Paul, Toulouse, France; J. Ring, Munich, Germany; J. Seneschal, Bordeaux, France; D. Simon, Bern, Switzerland; P. Spuls, Amsterdam, The Netherlands; J.F. Stalder, Nantes, France; A. Svensson, Malmö, Sweden; Z. Szalai, Budapest, Hungary; A. Täieb, Bordeaux, France; J.P. Thyssen, Copenhagen, Denmark; A. Torrelo, Madrid, Spain; M. Trzeciak, Gdansk, Poland; C. Vestergaard, Aarhus, Denmark; L. von Kobyletzki, Malmö, Sweden; S. Weidinger, Kiel, Germany; T. Werfel, Hannover, Germany; A. Wollenberg, Munich, Germany