DOI: 10.1111/j.1468-3083.2009.03415.x JEADV

ORIGINAL ARTICLE

ETFAD/EADV eczema task force 2009 position paper on diagnosis and treatment of atopic dermatitis

U Darsow,[†,‡,*] A Wollenberg,[§] D Simon,[¶] A Taïeb,[††] T Werfel,[‡‡] A Oranje,[§§] C Gelmetti,[¶¶] A Svensson,[†††] M Deleuran,[‡‡‡] A-M Calza,[§§§] F Giusti,[¶¶¶] J Lübbe,[§§§] S Seidenari,[¶¶¶] J Ring[†] for the European Task Force on Atopic Dermatitis/EADV Eczema Task Force[1]

[†]Department of Dermatology and Allergy Biederstein, Technische Universität München
[‡]Division of Environmental Dermatology and Allergy Helmholtz Center/TUM, Munich, Germany
[§]Department of Dermatology and Allergy, Ludwig-Maximilians-University, Munich, Germany
[¶]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[††]Service de Dermatologie, Hopital St André, Bordeaux, France
[‡‡]Hautklinik Linden, Department of Dermatology MHH, Hannover, Germany
[§§]Department of Pediatrics (Pediatric Dermatology Unit), ERASMUS MC, Rotterdam, The Netherlands
[¶¶]Instituto di clinica dermatologica prima e dermatologia pediatrica, Milan, Italy
[†††]Department of Dermatology, University Hospital UMAS, Malmö, Sweden
[‡‡‡]Department of Dermatology, Aarhus University Hospital, Aarhus, Denmark
[§§§]Clinique de Dermatologie, Hôpital Cantonal Universitaire, Genève, Suisse
[¶¶¶]Department of Dermatology, University of Modena and Reggio Emilia, Modena, Italy
*Correspondence: U Darsow. E-mail: ulf.darsow@lrz.tum.de

Abstract

Background The diagnosis of atopic dermatitis (AD) is made using evaluated clinical criteria. Management of AD must consider the symptomatic variability of the disease.

Methods EADV eczema task force developed its guideline for atopic dermatitis diagnosis and treatment based on literature review and repeated consenting group discussions.

Results and Discussion Basic therapy relies on hydrating topical treatment and avoidance of specific and unspecific provocation factors. Anti-inflammatory treatment based on topical glucocorticosteroids and topical calcineurin antagonists is used for exacerbation management and more recently for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, but the topical calcineurin inhibitors, tacrolimus and pimecrolimus are preferred in certain locations. Systemic anti-inflammatory treatment is an option for severe refractory cases. Microbial colonization and superinfection may induce disease exacerbation and can justify additional antimicrobial/antiseptic treatment. Systemic antihistamines (H1) can relieve pruritus, but do not have sufficient effect on eczema. Adjuvant therapy includes UV irradiation preferably of UVA1 wavelength or UVB 311 nm. Dietary recommendations should be specific and given only in diagnosed individual food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programmes have been proven to be helpful.

Received: 21 July 2009; Accepted: 22 July 2009

Keywords

atopic dermatitis, eczema, guideline, therapy

Conflict of Interest

Authors declare that they have no conflict of interest.

Introduction and definitions

Atopic dermatitis (AD, atopic eczema, eczema) is an inflammatory, chronically relapsing and intensely pruritic skin disease occurring often in families with atopic diseases (AD, bronchial asthma and/or allergic rhino-conjunctivitis). Eczema is a non-contagious inflammation of epidermis and dermis with characteristic clinical (itch, erythema, papule, seropapule, vesicle, squames, crusts, lichenification, in synchronous or

[1]See Appendix.

metachronous polymorphy) and dermatopathological (spongiosis, acanthosis, hyper- and parakeratosis, lymphocytic infiltrates and exocytosis, eosinophils) signs. With a prevalence of 2–5% (in children and young adults around 15%), 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: 'neurodermatitis', 'neurodermitis', 'endogenous eczema' are just few examples of current terms. Atopy is a strikingly common finding in these patients.[1] It can be defined as familial hypersensitivity of the skin and the mucosa to environmental substances, associated with increased production of immunoglobulin E (IgE) and/or altered pharmacological reactivity.[2,3] Recently, a new definition for atopy, restricted to IgE production, has been proposed: 'a personal or familial tendency to produce IgE antibodies in response to low doses of allergens, usually proteins, and to develop typical symptoms such as asthma, rhinoconjunctivitis or eczema/dermatitis'.[4]

The atopic diseases are genetically linked, and the concordance in monozygotic twins is 80% vs. 30% in dizygotic twins.[5] A multifactorial trait involving numerous gene loci on different chromosomes (3, 5 and 11) has been proposed.[6] Described genetic polymorphisms in AD involve mediators of atopic inflammation on different chromosomes; some of these may also play a role in respiratory atopy. Currently, the highest associations were shown with mutations in the filaggrin gene also associated with ichthyosis vulgaris, highlighting the predisposing barrier defect in AD patients (review in[7]).

In the first months of life, a yellowish desquamation on the scalp, known as 'cradle cap', may be a presentation of AD. The disease may then spread to the face and extensor surfaces of the arms and legs of toddlers, sometimes showing extensive oozing and crusting. Later on, the typical preferential pattern develops with eczematous involvement of flexures, neck and hands, accompanied by dry skin and skin barrier dysfunction reflected by an increased transepidermal water loss. Lichenification is a result of scratching and rubbing, and most frequently in adults this may result in the prurigo type of AD with predominant excoriated nodular lesions. Exacerbations often start as increased itch without visible skin lesions. This is followed by erythema, papules and infiltration.

The histopathology of acute AD lesions is characterized by epidermal hyperplasia, spongiosis occasionally leading to vesicle formation, by a marked inflammatory infiltrate composed of lymphocytes and histiocytes, variable number of eosinophils and mast cells in the upper dermis and by exocytosis of lymphocytes into the epidermis. Chronic, lichenified lesions show hyper- and parakeratosis, irregular epidermal hyperplasia, a moderate superficial dermal infiltrate of lymphocytes, histiocytes and some eosinophils and increased numbers of mast cells. Moreover, thickening of the papillary dermis and venular changes including endothelial hyperplasia and basement membrane thickening are observed.[8]

As these features are not specific for AD, routine histology is not a useful tool for diagnosing AD. In the absence of a specific diagnostic laboratory marker, mostly cutaneous stigmata of atopy have been used as diagnostic signs[1,3] – the diagnosis of AD is made clinically. Hanifin and Rajka stated three of four main criteria to be necessary: pruritus, typical morphology and distribution, chronic or chronically relapsing course and atopic personal or family history, in addition to the three minor criteria among a list of 21.[1] According to the UK working party,[9] who developed criteria especially suitable for epidemiological purposes but not in small children, 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 2 years, history of involvement of skin folds, generalized dry skin, other atopic diseases, visible flexural eczema.

Management of exacerbated AD is a therapeutic challenge, as it requires efficient short-term control of acute symptoms, without compromising the overall management plan that is aimed at long-term stabilization, flare prevention and avoidance of side-effects. Exacerbation may sometimes uncover relevant provocation factors, for example contact allergy or infection. Consequently, the initial workup must include a detailed inquiry on the circumstances of the flare, and a careful dermatological examination including lymph nodes, orifices and all skin folds. Professional attitude in face of exacerbated disease is setting the stage for future compliance. 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 medicine. Patient fears regarding treatment side-effects must be taken seriously with a constructive attitude. Instructing patients or parents about the necessary know-how regarding basic skin care is primordial.

Definition of management descriptive items

The chronic/relapsing nature of AD causes difficulties to propose and explain long-term management strategies (Fig. 1). Recent clinical trials addressing this issue have shown that there is a lack of consensus definitions for management procedures, i.e. 'proactive treatment' has been opposed to classic 'reactive treatment'.[10] There is a parallel need for health authorities to understand the claims of the industry for new products and reimbursement issues. The notion of intolerance or resistance to treatments is difficult to delineate except in case of well demonstrated contact allergy leading to topical eczema flares in loco. As quantitative rules for prescription of topicals are in general not applied (the amount of active products – mg/surface unit – important to prevent side-effects and assess efficacy is rarely included in trials), it is difficult to refer to an upper limit to define resistance.

The term of flare is difficult to delineate. Known stimuli including infections such as herpes simplex and *Staphylococcus aureus* infection, allergens or stress correspond to different adequate therapeutic responses from aetiological to symptomatic. There is no

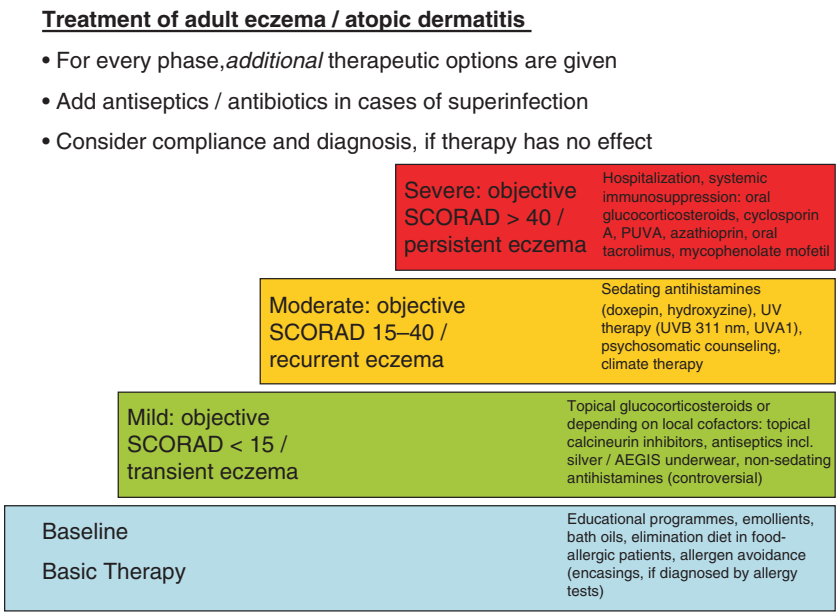

Figure 1 Treatment options for adult atopic dermatitis.

consensus on the diagnosis of an infectious flare due to *S. aureus*, except in case of clear cut clinical evidence of impetigo and toxinic rash. The definition of flares based on intensity scoring is difficult because the level of tolerance to pruritus can vary on a large scale of magnitude. Some patients with highly lichenified lesions report moderate pruritus or insomnia. The basal level of medication should be taken into account to measure variations or flares. Kinetics of variation in symptoms might be considered, but is practically difficult to monitor, except in case of use of a patient-oriented validated scoring system.

Table 1 Definitions of descriptive items for the management of AD (adapted from[135])

Flare: measurable increased extent or intensity of lesions in less than 2 weeks under continued treatment. Should ideally correspond to a significant increase in medical or patient-oriented clinical score (from 25%), or to the introduction of a new line of therapy
Remission: period without flare of at least 8 weeks without anti-inflammatory treatment (avoidance of irritants/allergens and emollients not included)
1. grade 1 remission: minimal treatment (avoidance, emollients)
2. grade 2 remission: 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
3. grade 3 remission: major treatment including phototherapy and immunosuppressants
Complete remission: absence of detectable lesions except residual dyschromia for at least 8 weeks without treatment. Irritant/allergen avoidance allowed
Intolerance to topical treatment: 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)
Resistance to topical treatment: physician's opinion after at least 2 weeks of therapy with an appropriate dosage of the treatment which has not changed or has aggravated the clinical score

Maintaining a good quality long-term remission is a shared objective in chronic disorders. A good nomenclature would help to compare data. Long-term remission without lesions and treatment is usually synonym of cure, but we need to define the time without intervention that may correspond to such a situation. Remission under minimal treatment (avoidance of irritants and allergens, emollients) is not comparable to remission under immunosuppressive agents. Some proposals are made in 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).[11]

Basic therapy for atopic dermatitis and skin care

Atopic dermatitis is a chronic condition. The treatment has to be planned with a long-term perspective. A systematic review of treatments of AD was published by Hoare *et al.*[12] However, regimens for basic/maintenance therapy are still awaiting validation.

Cleansing

The skin must be cleansed thoroughly, but gently and carefully to get rid of crusts and mechanically eliminate bacterial contaminants in the case of bacterial super-infection. Cleansers with or without antiseptics (the duration of action of some antiseptics is very limited, thus mechanical cleansing is probably more important) in non-irritant and low allergic formulas available in various galenic forms (syndets, aqueous solutions) may be used. The pH should be in a physiological cutaneous range (around 6). It is easier to

perform this first stage of gentle cleansing of skin on the nappy mattress rather than directly in the bath tube in infants. A further cleansing followed by a rapid rinse is performed in the bath (27–30°C). The short duration of the bath (only 5 min) and the use of bath oils (2 last minutes of bathing) are aimed at avoiding epidermal dehydration. Topical emollients are preferentially applied directly after a bath or a shower following gentle drying when the skin is still slightly humid. Although bathing seems very important, there is lack of evidence to prove that it is absolutely necessary.

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 compounds (cholesterol, essential fatty acids, ceramides) as well as the newly described filaggrin defect[7] enhance trans-epidermal water loss leading to epidermal micro-fissuring, which may also cause direct exposure of nerve endings. A better molecular and biochemical knowledge on this predisposing background should provide access to barrier improving topical agents. Promising studies have recently been reported along this line.[13] The cost of high quality allergy-safe emollient therapies often restrict their use because such therapies are considered to be non-prescription drugs and the quantities required are usually high (150–200 g per week in young children, up to 500 g in adults). Their direct use on inflamed skin is poorly tolerated and it is better to treat the acute flare first as outlined below. The use of a barrier ointment that can also be used as bath oil and shower gel is even better.

Hydration of the skin is usually maintained by at least twice daily application of moisturizers with a hydrophilic base containing approximately 5% urea, if tolerated. Emulsions or micellar solutions as well as bath oils may also help to reduce the flares. Use of emollients improves dryness and subsequently pruritus during the treatment of AD and especially improves the barrier function. There is limited evidence-based proof for the use of emollients. A randomized controlled trial by Grimalt showed that the correct use of emollients reduced the amount of corticosteroids used.[14] Emollients containing potentially allergenic proteins such as peanut or oat should be avoided in the most vulnerable age group before the age of 2.[15]

Avoidance strategies on the basis of allergy diagnosis

Atopic dermatitis is an inflammatory skin disorder with a relapsing course, associated to unspecific skin hyper-reactivity, IgE production and immediate or delayed hyper-sensitivity to environmental allergens, such as food and inhalants. Irritant factors comprising chemicals and physical agents may complicate the course of the disease. Finally, contact sensitization to chemicals is frequently found in AD. Diagnosis of the disease has to be distinguished from diagnosis of individually relevant trigger factors. In some centres, allergic exploration is limited to severe cases without response to classical topical treatment.

Food allergens

Among food allergens, cow's milk, hen's egg, wheat, soy, tree nuts and peanuts are most frequently responsible for eczema or exacerbation in infancy and toddlers.[16] In older children, adolescents and adults, pollen related food allergy should be taken into account.[17,18] When challenging AD patients with food, one can observe either early reactions, such as urticaria, gastrointestinal or respiratory symptoms occurring within 120 min after the administration of the allergens, or late phase responses, manifesting as eczematous lesions, occurring after 2–48 h or some days. After oral food challenge, about 50% of children with AD who reacted to food showed both immediate and delayed reactions and 15% showed worsening of eczema only.[19] This study also showed that the personal history is often not of great help predicting late reactions to food with a positive predictive value of only 30% as opposed to 80% for immediate reactions.

Sensitizations to food can be investigated by means of *in vivo* tests [skin prick tests (SPT), prick-prick tests] and *in vitro* tests (serum specific IgE). In addition, patch tests proved to be useful for studying delayed food-related skin responses.

In vitro tests are valuable when SPT cannot be applied (e.g. dermographism or UV- and drug induced skin hypo-reactivity, eczema at the test site, lack of compliance for SPT in infancy, etc.). Moreover, *in vitro* specific IgE to food allergens give better quantitative data for the grade of sensitization which helps to estimate the probability of the risk of a clinical reaction (although precise decision points are not available), and it offers the opportunity to test single recombinant allergens which may have a better diagnostic specificity than testing with food extracts for some foods (e.g. omega-5-gliadin in wheat allergy, Gly m 4 in pollen-related soy allergy).

Atopy patch tests (APTs) are performed with self-made food material applied to the back with large test chambers for 48–72 h. Food APT is not standardized for routine use.[20] So far, APTs have demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, egg, cereals and peanuts in AD patients.[21–27] Whereas immediate-type reactions are associated with SPT positivity; delayed ones are related to positive responses to APTs. However, food challenge is not replaced by patch testing.[28] The double-blind placebo-controlled food challenge is considered the gold standard for diagnosing food allergy.[29] In AD, the evaluation of delayed reactions after 24 or 48 h by trained personal is mandatory as stated by a recent position paper of the EAACI.[30] Challenge tests based on repeated exposure to food (for 7 days) appear to be practical and enable the assessment of delayed

adverse responses.[21,22,26,27] The major flaw is that they do not offer the opportunity to exclude placebo reactions and/or coincidental influences of other trigger factors of AD during the prolonged challenge period.

Aeroallergens

Clinical observations indicate that aeroallergens are relevant trigger factors in AD patients. Exacerbations of eczematous lesions after skin contact or inhalation have been described, and an improvement can be observed after allergen avoidance, especially with regard to house dust mites by means of acaricides, bedcovers, mattress encasings and vacuum cleaning.

Routine diagnostic workup of suspected allergy to aeroallergens includes *in vivo* and *in vitro* detection of specific IgE by means of SPT or serological assays. However, both techniques have a low predictive value.

Patch testing for AD patients with aeroallergens (APT),[31,32] was performed with house dust mites, pollen and animal dander, obtaining different positivity rates (15–100%) according to patch test materials and modalities.[23,32–36] 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. A recent position paper of EAACI[20] points out the indications of APT. In some European countries, aeroallergen preparations for APT are available from different manufacturers. As still no gold standard for provocation of eczema in aeroallergen-mediated AD exists, specific avoidance strategies should be considered in patients reacting to APTs (Table 2).

Table 2 List of aggravating factors and counselling for AD patients

• Clothing: avoid skin contact with irritating fibres (wool, large fibres textiles); do not use tight and too warm clothing to avoid excessive sweating. New non-irritating clothing designed for AD children is currently evaluated
• 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. Usually helpful because of improvement of epidermal barrier. Encourage summer holidays in 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
Maintain breast feeding until four months if possible
Otherwise normal diet, unless an allergy workup has proven the need to exclude a specific food
• Indoor aeroallergens
House dust mites
Use adequate ventilation of housing. Keep the rooms well aerated even in winter
Avoid wall to wall carpeting
Remove dust with a wet sponge
Vacuum with an adequate filtered cleaner once a week floors and upholstery
Avoid soft toys in bed (cradle), except washable ones
Wash bed sheets at a temperature higher than 55° every 10 days
Bed and pillow encasings in GoreTex or similar
• Furred pets: advise to avoid. If allergy is demonstrated, be firm on avoidance measures
• Pollen: 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

Allergen-specific immunotherapy

The efficacy of specific immunotherapy in AD has been shown in a number of case reports and smaller cohort studies (reviewed by Bussmann *et al.*[37]), and more recently in a larger multicentre trial with house dust mite immunotherapy.[38] As a result of these data, it became clear that the SIT can be applied for the treatment of allergic rhinitis or mild asthma and also in those patients who suffer in addition from AD as eczema was obviously not worsened during or after SIT. More larger prospective studies are now being performed which shall respond to the question if AD alone may be an indication for the initiation of SIT.

Contact allergy

The role of contact allergy in AD patients is frequently underestimated.[39,40] The frequency of contact sensitization in AD, ranging from 41% to 64% according to recent observations, supports the importance of systematic patch testing in atopic patients, adults and children. The most common contact sensitizers are metals, fragrance, neomycin and lanolin. Therefore, preventive measures from an early age should be introduced to avoid contact with nickel containing objects, perfumed cosmetics and products or topical medication including lanolin and neomycin in AD patients.

Contact sensitization may worsen the skin condition of atopic patients and influence the course of the atopic disease. Moreover, sensitized atopic subjects may respond to very low concentrations of contact allergens, because of their impaired skin barrier function and hyper-reactivity to irritant stimuli enhancing contact reactions. In fact, SLS pretreatment of nickel patch test sites proved to induce an earlier onset of the inflammatory reaction and a more marked cutaneous damage in atopic nickel-sensitive patients in comparison with nickel sensitive non-atopics, followed by a more intense allergic response, probably due to an increased allergen penetration and/or the summation of immune and non-immune mechanisms.[41]

Atopic patients run a significant risk of developing contact dermatitis, especially on the hands, when exposed to occupational

irritant factors, i.e. chemicals, water or soil. Atopy amplifies the effects of irritant and allergen exposure in occupations such as hairdressers, cleaners, metalworkers, mechanics and nurses, where hand eczema is a very common disease.[41] Based on these data, preventive strategies should be developed and optimized to reduce the incidence of occupational dermatitis in AD patients.

Topical anti-inflammatory treatment

Topical treatment

Effective topical therapy depends on three fundamental principles: sufficient strength, sufficient dosage and correct application. Topical treatment should always be applied on hydrated skin, especially when using ointments. The emollient should be applied first when it is a cream, 15 min before the anti-inflammatory topical is applied and when it is an ointment 15 min after. Patients with acute, oozing and erosive lesions, and children in particular, sometimes do not tolerate standard topical application, and may first be treated with 'wet wraps' until the oozing stops. They are highly effective in acute eczema and improve tolerance. The use of wet-wrap dressings with diluted corticosteroids for up to 14 days (usual is rather up to 3 days) is a safe crisis intervention treatment of severe and/or refractory AD with temporary systemic bioactivity of the corticosteroids as the only reported serious side-effects.[42,43] 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 eczema may require a few days with higher treatment frequency.

By tradition, anti-inflammatory topical therapy has been administered to lesional skin only and has been stopped or tapered down once visible lesions were cleared. This traditional, reactive approach has in the last years been challenged by the proactive treatment concept, which is defined as a combination of predefined, long-term, low dose, anti-inflammatory treatment applied to previously affected areas of skin in combination with liberal use of emollients on the entire body and a predefined appointment schedule for clinical control examinations.[10,44] The proactive, usually twice weekly treatment regimen is started after all lesions have successfully been treated by an intensive, usually twice daily treatment approach in addition to ongoing emollient therapy for previously unaffected skin. Clinical trial data are available for a number of steroid products as well as for tacrolimus ointment.[10,44]

Corticosteroids

Topical glucocorticosteroids are a first-line anti-inflammatory treatment, applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flare). Numerous substances are available in a variety of formulations. Evidence-based anti-inflammatory effects in AD were reported by different investigators.[12,44–46] With mild disease activity, a small amount of topical corticosteroids twice to thrice weekly (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 allows a good maintenance keeping SCORAD values below 15–20. Such monthly amounts of even potent topical steroids usually do not have adverse systemic or local effects.

Topical corticosteroids are grouped by potency, which should be known to prescribers. Potent and very potent corticosteroids (group III and IV) are more likely to cause depression of adrenal function than group I (mild) and II (moderate strength) treatments, but their systemic effects will decrease more quickly due to more rapid restitution of the skin barrier.[47,48] Itch is the key symptom for evaluation of response to treatment, and tapering should not be initiated before the itch has disappeared. Dose tapering should be gradual to avoid withdrawal rebound; tapering strategies consist in using a less potent corticosteroid on a daily base, or keeping a more potent one while reducing the frequency of application (intermittent regimen). One well-conducted, correctly dosed treatment per day is sufficient.[49,50] The most constructive way to spare steroids and avoid steroid-related side-effects is not to spare them during acute flares, but through consequent baseline emollient skin care combined with early anti-inflammatory intervention to stabilize the disease and prevent treatment-intensive flares.[51]

Topical calcineurin inhibitors

The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, are licensed for topical eczema treatment. Various aspects of these drugs have been reviewed in detail.[52] The efficacy of both formulations has been demonstrated against placebo in clinical trials for short-term[53,54] and long-term use of these substances.[55,56] In addition, proactive tacrolimus ointment therapy has been shown to be safe and effective for up to 1 year in reducing the number of flares and improving the quality of life in adult patients and children.[57,58] The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity,[59] while the latter is clearly more active than 1.0% pimecrolimus cream.[60]

Safety data of both topical calcineurin inhibitors have been reported in many clinical trials, demonstrating the safety of these drugs in daily routine use. The most frequently observed side-effect is a transient warmth sensation or transient burning at the application site during the first days of application.[53,60] It starts about 5 min after each application of the drug and may last up to 1 h, but intensity and duration typically decrease within 1 week to zero.[61] Generalized viral infections such as eczema herpeticum (EH) or eczema molluscatum (EM) have been observed during topical calcineurin inhibitor treatment,[62,63] but a high number of clinical trials failed to demonstrate an increased frequency (reviewed in [64–66]). In contrast to corticosteroids, none of the topical calcineurin inhibitors induces skin atrophy.[67,68] This favours their use over topical corticosteroids 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 and preclinical data do not indicate an increased risk of the induction of lymphoma over a period of 6 years[69] or photocarcinogenicity for topical calcineurin inhibitors,[70] but since the continuous oral administration of the calcineurin inhibitor cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection e.g. with sunscreens has been advised.[61] The use of topical calcineurin inhibitors under wet wraps or on erosive lesions may increase systemic absorption.

The efficacy of long-term monotherapy with tacrolimus ointment has been shown in children and adults.[59,71] Less data are available for children under 2 years of age.[72] Pimecrolimus cream has been studied in infants and children in a combination regimen with topical corticosteroids,[73,74] the latter being given if a flare occurred. Both topical calcineurin inhibitors are approved in the EU from 2 years of age and above. High quality long-term safety data have recently been published from a 4-year tacrolimus and 26 weeks pimecrolimus study.[75,76] The cost effectiveness of proactive therapy with topical tacrolimus has been addressed in a recent study,[77] whereas the cost effectiveness of first-line treatment with topical calcineurin inhibitors has not been shown conclusively.

Antihistamines

Systemic antihistamines (anti-H1) are widely used in acute flares against itch; however there are few controlled studies.[78] Antihistamines may be helpful to decrease pruritus and permit sleep during flares. In this setting, sedative anti-H1 molecules such as hydroxyzine are frequently considered as more helpful than recent less sedative drugs. Concerning the newer non-sedating H1R specific antihistamines, controlled studies did not show substantial effects on eczema. Ongoing studies concentrate on the blockade of alternative histamine receptors which may be more important in eczema.

Anti-bacterial and antimycotic therapy

A number of defects in innate cutaneous immunology may explain the high rate of cutaneous colonization with *S. aureus* (up to 90% in moderate to severe eczema) in AD.[79] Antibiotic eradication of *S. aureus* may therefore not always be an appropriate long-term strategy, especially with regard to the increasing prevalence of antibiotic resistance.[80–82] Therefore, topical antibiotics should not be used for longer periods in the treatment of AD. However, there is evidence for an association of *S. aureus*-derived superantigens with disease exacerbation,[83,84] supporting early observations that the density of *S. aureus* colonization in AD is significantly correlated with clinical severity,[85] and that patients with severe AD may improve (but not be cured) by antistaphylococcal treatment.[86] In general, improving eczema with anti-inflammatory regimen (i.e. TCS, TCI, UV) decreases staph colonization. This led to the current clinical concept that patients with high numbers of colonizing *S. aureus* can benefit from combination treatment with corticosteroids and antibacterial treatment, in most cases using topical antiseptics like triclosan, chlorhexidine or crystal violet 0.3 %.[87,88] Only when acute flares of AD are frequently associated with clinical signs of bacterial impetiginization, such as oozing, pustules and fissures, exacerbated disease may justify treatment with an antibiotic.[87,89] Apart from specific indications such as overt secondary infection or presence of beta-haemolytic streptococci,[90,91] treatment of eczema with antibiotics had no effect in regards to clinical improvement and sparing of steroids[92] and should therefore not be performed.

The use of silver-coated textiles and silk fabric with the durable antimicrobial finish AEGIS ADM 5772/S can reduce *S. aureus* colonization and eczema severity.[93,94] These new options are still under investigation. There is much concern about the safety of these silver-coated textiles in infants and toddlers.

Other secondary infections, such as yeasts, dermatophytes and streptococcal infections have also been implicated as disease factors in AD (for a review, see [80]). Intense, fleshy erythema in skin folds of children with a flare of AD may warrant a search for streptococcal skin infection. In general, signs of secondary infections should be treated if present. Ketoconazole and ciclopiroxolamine are proposed for topical treatment of 'head and neck' AD, often associated with *Malassezia sympodialis* superinfection. Systemic ketoconazole[95] and topical ciclopiroxolamine[96] have been shown to improve eczema significantly within 4 weeks in placebo-controlled trials in patients with 'head–neck–shoulder dermatitis'.

Anti-viral therapy

Viral infections are occurring more frequently in AD patients than in normal individuals, with a tendency to disseminated, widespread disease. The latter is named after the causative virus as eczema molluscatum (EM), eczema vaccinatum or eczema herpeticum (EH).[97] A disseminated, distinctly monomorphic eruption of dome-shaped vesicles, accompanied by fever, malaise and lymphadenopathy is suggestive for EH. Physicians and patients should be aware of the symptoms, as unintentional anti-inflammatory instead of antiviral treatment may favour a progression from herpes simplex to EH. EH has been described following corticosteroid and calcineurin inhibitor therapy, but recent data indicate that patients with severe, untreated AD, a high total serum-IgE and early onset of AD are at risk for EH, whereas pretreatment with topical corticosteroids does not imply a risk.[98] The clinical diagnosis should be confirmed by PCR, electron microscopy, immunofluorescence tests or viral culture. A direct Tzanck smear is quicker, but not so specific. The mainstay of EH therapy is prompt systemic antiviral chemotherapy with i.v. acyclovir, but a number of alternative treatment modalities exist.[97]

Atopic dermatitis patients, in particular children, may develop widespread EM with up to several hundred umbilicated small skin-coloured papules.[97] Although EM lesions resolve spontaneously, treatment speeds healing and prevents spreading by auto- and heteroinoculation. In addition to mild anti-inflammatory treatment,[99] limited numbers of lesions may be destroyed with a small curved forceps, removed by curettage or destroyed by

cryotherapy or carbon dioxide laser vaporization.[97] Topical application of imiquimod or other topical immunostimulatory drugs shows promising results,[100] but is expensive and not always well tolerated.

Phototherapy

As most patients affected by AD improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AD. When prescribed, phototherapy is usually a part of a total treatment plan, i.e. a second-level treatment used especially in adults and much less in children. Phototherapy in children younger than 12 years should not be applied. The mechanism of action targets immunomodulation through apoptosis of inflammatory cells, inhibition of Langerhans cells and alteration of cytokine production.[101] In addition, UV has an antimicrobial effect reducing the colonization of *S. aureus*,[102] due to its anti-inflammatory effect and improves skin barrier.[103]

Present UV sources include equipments able to emit selective spectres of radiations:

- Broadband UV (UVA + UVB = 290–400 nm)
- Narrow-band UVB (nbUVB = peak:311–313 nm)
- UVA1 (340–400 nm).

Treatment with longer wavelengths has not been studied for AD and should therefore not be applied.

As a rule, phototherapy is not indicated in the acute stage of AD (except UVA1, which is also effective in managing AD flares), but is more apt to treat chronic, pruritic, lichenified forms and should not be prescribed in those patients who experience a worsening of their dermatosis during sun exposure. In practice, the choice of a different UV treatment is limited by the availability of the phototherapy equipments: e.g. UVA1 are expensive to buy and to maintain. The biggest drawbacks of UV therapy are that the patient must travel between 3 and 5 times per week and for 6–12 weeks to a site that offers this therapy. In addition, UV light does not effectively treat hairy areas as scalp and skin folds.

In short, taking into account the individual tolerability, nbUVB has been indicated for chronic-moderate forms of AD[104] and is currently preferred to broadband UV because it is less erythemogenic, while high dose UVA1 has been prescribed for more severe phases.[104] Medium dose UVA1 appears to be similar in terms of efficacy as narrow band UVB.[105,106] Topical steroids and emollients should be considered at the beginning of phototherapy to reduce a possible flare-up, while topical immunosuppressors as tacrolimus and pimecrolimus should be avoided. UV can also be combined with a previous (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 for development of skin cancer, together with the proven prematurely ageing of the skin. UV therapy has to comply with special requirements with regard to personnel, documentation, UV protection especially of the eyes, contraindications and technical aspects.

Photochemotherapy is not the first choice of AD because of the proven carcinogeneity and the fact that most AD patients are young. During photochemotherapy, patients must wear UVA-blocking sunglasses and also after treatment for 1 or 2 days when exposed to sunlight because psoralens are eliminated slowly. While simple UV regimens are generally well tolerated (a transient sensation of warmth should be considered normal), 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,[107] so the risk/benefit ratio of this treatment must be carefully weighted.

In conclusion, phototherapy can improve, and even clear, AD; it can decrease bacterial colonization and reduce the strength and/or the amount of needed topical anti-inflammatory drugs, but the beneficial effects vary from person to person. New devices as 308 nm monochromatic excimer light are promising but still experimental and can treat only limited surfaces.[108]

Systemic anti-inflammatory therapy

Resistance to well-conducted topical therapy is rare, and systemic anti-inflammatory treatment should be limited to severe cases where the potential of topical treatment (or of patient compliance) has been exhausted. An actual overview of the different options has recently been published.[109] Corticosteroids are rapidly effective, but should only be used for a few weeks, for severe acute exacerbations, due to the many long-term side-effects. In severe chronic cases starting another systemic anti-inflammatory therapy is considered while tapering the corticosteroid.

The usefulness of cyclosporin (3–5 mg/kg/day) and azathioprine (2.5 mg/kg/day) has been well documented in clinical trials with children and adults.[110–113] Cyclosporin A therapy is rapidly effective, but has a narrow therapeutic index and requires a close follow-up for signs of renal impairment. It is the approved substance for systemic treatment of AD in many countries.

Azathioprine has a slower onset of action and is not always well tolerated. Low TPMT (thiopurine-methyltransferase) activity is associated with an increased myelotoxicity of azathioprine, but patients at risk can be identified by pretreatment screening for TPMT activity.[112]

Mycophenolate mofetil (2 g/day) seems to offer a comparatively more favourable security profile, and its usefulness in severe AD is documented in both prospective and retrospective studies,[114–116] but remains to be assessed in larger randomized trials.

Methotrexate is used by many clinicians as an alternative treatment. Only a few studies have documented its effect and randomized trials are needed.[117]

Biologics and probiotics

Biological agents (biologicals) present new therapeutic tools in the treatment of recalcitrant AD. They specifically target inflammatory cells and mediators, respectively, and thus may inhibit pathogenically relevant pathways. A number of case reports and pilot studies

have been published recently, however representative, randomized, placebo controlled studies evaluating the efficacy and safety of biologicals in AD are still not available.

Approaches resulting in reduced T-cell activation using agents such as alefacept [fusion protein of lymphocyte function antigen (LFA)-3 (CD58) and immunoglobulin (Ig)G], rituximab (anti-CD20 antibody) and efalizumab (anti-CD11a antibody, no longer available) have been shown to be effective in patients with moderate to severe AD. Alefacept (12 × 15 mg, IM, weekly), which inhibits costimulation and induces apoptosis of T cells, lead to a significant improvement of symptoms and reduction in steroid therapy.[118] Another study reported a clinical improvement in six of nine patients.[119] Interestingly, the depletion of B cells by rituximab (2 × 1000 mg, IV) resulted in a rapid and sustained reduction in skin inflammation, suggesting an important role of B cells in the pathogenesis of AD.[120] Upon therapy with efalizumab (12 × 0.7–1 mg/kg weekly, SC), which inhibits T-cell recruitment, a significant decrease in symptoms has been reported.[121] Anti-IgE (omalizumab) therapy showed beneficial effects in patients with moderate to severe AD;[122–124] however the registered maximal dosage might not be sufficient in patients with extremely elevated IgE levels.[125] Mepolizumab (anti-IL-5 antibody, 2 × 750 mg 1 week apart) almost completely depletes blood eosinophils and had a moderate clinical effect in a short-term study with two infusions per patient.[126] Unfortunately a long-term study has not been performed with anti-IL-5 antibodies after these promising results. Anti-TNF-alpha (infliximab) has been shown to have short-term effects in patients with severe AD.[127]

Treatment regimens with probiotics aim to modulate the microflora in the gut to stimulate the immune response towards an allergy protecting, T-helper 1-biased immune reaction.[128] Unfortunately, no effects of probiotics in the treatment of mild or moderate to severe AD have been found in controlled studies after first promising reports in open studies.[129,130] Moreover, according to a number of recent studies, there is also no evidence anymore that prenatal and postnatal application of probiotics reduces the likelihood of having AD during the first two years of life outside Finland.[131,132]

Educational programmes and counselling

This time-consuming task is particularly important (Table 2). Much time is needed to answer the questions of the patient or parents. The bottom line is to allow the patient or the child and family to lead a close to normal life, avoiding unnecessary measures and avoidable constraint. Early detection and prevention of bronchial asthma in infants with AD are part of the global management. Vaccinations, including those against measles in hen's egg allergy are safe,[133] the only restriction being the quality of skin care to avoid superinfection at injection sites and with vaccination against influenza and yellow fever in highly sensitized egg-allergic children.

In the last decade, education programmes for patients and parents were established in different European countries. Standardized interdisciplinary programmes involving dermatologists, paediatricians, psychologists/psychosomatic counsellors and dietary counselling have been demonstrated to improve subjective and objective symptoms, and optimize medication use in patients, and result in a significant gain in quality of life.[134] Participation in one of these programmes is highly encouraged.

References

1 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; **92**(Suppl.): 44–47.
2 Ring J, Przybilla B, Ruzicka T, eds. *Handbook of Atopic Eczema*, 2nd edn. Springer, Heidelberg, 2006.
3 Ring J. *Allergy in Practice*. Springer, Heidelberg, 2004.
4 Johansson SGO, Bieber T, Dahl R *et al.* Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol* 2004; **113**: 832–836.
5 Schultz-Larsen F. *Atopic Dermatitis. Etiological Studies Based on a Twin Population*. Laegeforeningens, Kopenhagen, 1985.
6 Cookson WO, Moffatt MF. The genetic of atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2002; **2**: 383–387.
7 Weidinger S, O'Sullivan M, Illig T *et al.* Filaggrin mutations, atopic eczema, hay fever, and asthma in children. *J Allergy Clin Immunol* 2008; **121**: 1203–1209.
8 Mihm MC, Soter NA, Dvorak HF, Austen KF. The structure of normal skin and the morphology of atopic eczema. *J Invest Dermatol* 1976; **67**: 305–312.
9 Williams HC, Burney PJG, Pembroke AC, Hay RJ. Validation of the UK diagnostic criteria for atopic dermatitis in a population setting. *Br J Dermatol* 1996; **135**: 12–17.
10 Wollenberg A, Bieber T. Proactive therapy of atopic dermatitis – an emerging concept. *Allergy* 2009; **64**: 276–278.
11 Taïeb A. Dermatite atopique: définition, épidémiologie, histoire naturelle, scores de gravité. *Ann Dermatol Venereol* 2005; **132**: 1535–1543.
12 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.
13 Chamlin SL, Frieden IJ, Fowler A *et al.* Ceramide-dominant, barrier-repair lipids improve childhood atopic dermatitis. *Arch Dermatol* 2001; **137**: 1110–1112.
14 Grimalt R, Mengeaud V, Cambazard F, Study Investigators' Group. The steroid-sparing effect of an emollient therapy in infants with atopic dermatitis: a randomized controlled study. *Dermatology* 2007; **214**: 61–67.
15 Boussault P, Léauté-Labrèze C, Saubusse E *et al.* Oat sensitization in children with atopic dermatitis: prevalence, risks and associated factors. *Allergy* 2007; **62**: 1251–1256.
16 Werfel T, Breuer K. Role of food allergy in atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2004; **4**: 379–385.
17 Breuer K, Wulf A, Constien A, Tetau D, Kapp A, Werfel T. Birch pollen-related food as a provocation factor of allergic symptoms in children with atopic eczema/dermatitis syndrome. *Allergy* 2004; **59**: 988–994.
18 Reekers R, Busche M, Wittmann M, Kapp A, Werfel T. Birch pollen-related foods trigger atopic dermatitis in patients with specific cutaneous T-cell responses to birch pollen antigens. *J Allergy Clin Immunol* 1999; **104**: 466–472.
19 Breuer K, Heratizadeh A, Wulf A *et al.* Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004; **34**: 817–824.
20 Turjanmaa K, Darsow U, Niggemann B, Rancé F, Vanto T, Werfel T. EAACI/GA2LEN Position Paper: Present status of the atopy patch test – position paper of the Section on Dermatology and the Section on Pediatrics of the EAACI. *Allergy* 2006; **61**: 1377–1384.

21 Isolauri E, Turjanmaa K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; **97**: 9–15.
22 Majamaa H, Moisio P, Holm K, Turjanmaa K. Wheat allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999; **54**: 851–856.
23 Darsow U, Ring J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000; **25**: 544–551.
24 Niggemann B. The role of the atopy patch test (APT) in diagnosis of food allergy in infants and children with atopic dermatitis. *Pediatr Allergy Immunol* 2001; **12**: 37–40.
25 Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggeman B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenge in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; **103**: 548–553.
26 Strömberg L. Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002; **91**: 1044–1049.
27 Seidenari S, Giusti F, Bertoni L, Mantovani L. Combined skin and patch testing enhances identification of peanut-allergic patients with atopic dermatitis. *Allergy* 2003; **58**: 495–499.
28 Mehl A, Rolinck-Werninghaus C, Staden U *et al.* The atopy patch test in the diagnostic workup of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006; **118**: 923–929.
29 Bindslev-Jensen C. Standardization of double-blind, placebo-controlled food challenges. *Allergy* 2001; **56**: 75–77.
30 Werfel T, Ballmer-Weber B, Eigenmann PA *et al.* Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA2LEN. *Allergy* 2007; **62**: 723–728.
31 Mitchell EB, Crow J, Chapman MD, Jouhal SS, Pope FM, Platts-Mills TA. Basophils in allergen induced patch test sites in atopic dermatitis. *Lancet* 1982; **I**: 127–130.
32 Ring J, Kunz B, Bieber T, Vieluf D, Przybilla B. The ''atopy patch test'' with aeroallergens in atopic eczema. *J Allergy Clin Immunol* 1989; **82**: 195.
33 Seidenari S, Manzini BM, Danese P. Patch testing with pollen in patients with atopic dermatitis and mucosal atopy. *Contact Derm* 1992; **27**: 25.
34 Darsow U, Vieluf D, Ring J. Atopy patch test with different vehicles and allergen concentration. An approach to standardization. *J Allergy Clin Immunol* 1995; **95**: 677–684.
35 Seidenari S, Giusti F, Pellicani G, Bretoni L. Frequency and intensity of responses to mite patch tests are lower in non atopic subjects in respect to patients with atopic dermatitis. *Allergy* 2003; **58**: 426–429.
36 Darsow U, Laifaoui J, Bolhaar S *et al.* The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004; **59**: 1318–1325.
37 Bussmann C, Böckenhoff A, Henke H, Werfel T, Novak N. Does allergen-specific immunotherapy represent a therapeutic option for patients with atopic dermatitis? *J Allergy Clin Immunol* 2006; **118**: 1292–1298.
38 Werfel T, Breuer K, Ruéff F *et al.* Usefulness of specific immunotherapy in patients with atopic dermatitis and allergic sensitization to house dust mites: a multi-centre, randomized, dose-response study. *Allergy* 2006; **61**: 202–205.
39 Manzini BM, Ferdani G, Simonetti V, Donini M, Seidenari S. Contact sensitization in children. *Contact Derm* 1998; **15**: 12–17.
40 Mortz CG, Andersen KE. Allergic contact dermatitis in children and adolescents. *Contact Derm* 1999; **41**: 121–130.
41 Seidenari S, Giusti F. Skin sensitivity, interindividual factors: atopy. In van deer Valk PMG, Maibach H, eds. *The Irritant Contact Dermatitis Syndrome*. CRC Press, Boca Raton, FL, 2006: 266.
42 Devillers AC, Oranje AP. Efficacy and safety of 'wet-wrap' dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature. *Br J Dermatol* 2006; **154**: 579–585.
43 Schnopp C, Holtmann C, Stock S *et al.* Topical steroids under wet-wrap dressings in atopic dermatitis-a vehicle-controlled trial. *Dermatology* 2002; **204**: 56–59.
44 Van der Meer JB, Glazenburg EJ, Mulder PG, Eggink HF, Coenraads PJ. The management of moderate to severe atopic dermatitis in adults with topical fluticasone propionate. The Netherlands Adult Atopic Dermatitis Study Group. *Br J Dermatol* 1999; **140**: 1114–1121.
45 Hanifin J, Gupta AK, Rajagopalan R. Intermittent dosing of fluticasone propionate cream for reducing the risk of relapse in atopic dermatitis patients. *Br J Dermatol* 2002; **147**: 528–537.
46 Berth-Jones J, Damstra RJ, Golsch S *et al.* Twice weekly fluticasone propionate added to emollient maintenance treatment to reduce risk of relapse in atopic dermatitis: randomised, double blind, parallel group study. *BMJ* 2003; **326**: 1367.
47 Feiwel M, Munro D, James V. Effect of topically applied 0.1% betamethasone valerate ointment on the adrenal function of children. In Jadassohn W, Schirren CG eds. *Thirteenth congress of International Dermatology*. Springer, Berlin, 1968: 202–204.
48 Walsh P, Aeling J, Huff L, Weston W. Hypothalamus-pituitary-adrenal axis suppression by superpotent topical steroids. *J Am Acad Dermatol* 1993; **29**: 501–503.
49 Queille C, Pommarede R, Saurat J-H. Efficacy versus systemic effects of six topical steroids in the treatment of atopic dermatitis of childhood. *Pediatr Dermatol* 1984; **1**: 246–253.
50 Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003; **21**: 193–200.
51 Eichenfield L, Hanifin J, Beck L *et al.* Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003; **111**: 608–616.
52 Bornhövd E, Burgdorf WHC, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. *J Am Acad Dermatol* 2001; **45**: 736–743.
53 Ruzicka T, Bieber T, Schöpf E *et al.* A short-term trial of tacrolimus ointment for atopic dermatitis. *N Engl J Med* 1997; **337**: 816–821.
54 Van Leent EJ, Graber M, Thurston M, Wagenaar A, Spuls PI, Bos JD. Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. *Arch Dermatol* 1998; **134**: 805–809.
55 Reitamo S, Wollenberg A, Schöpf E *et al.* Safety and efficacy of 1 year of tacrolimus ointment monotherapy in adults with atopic dermatitis. *Arch Dermatol* 2000; **136**: 999–1006.
56 Meurer M, Fölster-Holst R, Wozel G, Weidinger G, Jünger M, Bräutigam M. Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology* 2002; **205**: 271–277.
57 Wollenberg A, Reitamo S, Girolomoni G *et al.* Proactive treatment of atopic dermatitis in adults with 0.1% tacrolimus ointment. *Allergy* 2008; **63**: 742–750.
58 Thaci D, Reitamo S, Gonzalez Ensenat MA *et al.* Proactive disease management with 0.03% tacrolimus ointment for children with atopic dermatitis: results of a randomized, multicentre, comparative study. *Br J Dermatol* 2008; **159**: 1348–1356.
59 Reitamo S, Rustin M, Ruzicka T *et al.* Efficacy and safety of tacrolimus ointment compared with hydrocortisone butyrate ointment in adult patients with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 547–555.
60 Luger T, Van Leent E, Graeber M *et al.* SDZ ASM 981: an emerging safe and effective treatment for atopic dermatitis. *Br J Dermatol* 2001; **144**: 788–794.
61 Bornhövd EC, Burgdorf WHC, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. *Curr Opin Investig Drugs* 2002; **3**: 708–712.

62 Lübbe J, Pournaras CC, Saurat JH. Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. *Dermatology* 2000; **201**: 249–251.
63 Wetzel S, Wollenberg A. Eczema molluscatum in tacrolimus treated atopic dermatitis. *Eur J Dermatol* 2004; **14**: 73–74.
64 Wahn U, Bos J, Goodfield M *et al.* Efficacy and safety of pimecrolimus cream in the long-term management of atopic dermatitis in children. *Pediatrics* 2002; **110**: 1–8.
65 Lübbe J. Klinische Erfahrungen mit topischen Calcineurininhibitoren in der Praxis. *Hautarzt* 2003; **54**: 432–439.
66 Bornhövd E, Wollenberg A. Topische Immunmodulatoren zur Ekzembehandlung. *Allergo J* 2003; **12**: 456–462.
67 Reitamo S, Rissanen J, Remitz A *et al.* Tacrolimus ointment does not affect collagen synthesis: results of a single-center randomized trial. *J Invest Dermatol* 1998; **111**: 396–398.
68 Queille-Roussel C, Paul C, Duteil L *et al.* The new topical ascomycin derivative SDZ ASM 981 does not induce skin atrophy when applied to normal skin for 4 weeks: a randomized, double-blind controlled study. *Br J Dermatol* 2001; **144**: 507–513.
69 Arellano FM, Wentworth CE, Arana A, Fernández C, Paul CF. Risk of lymphoma following exposure to calcineurin inhibitors and topical steroids in patients with atopic dermatitis. *J Invest Dermatol* 2007; **127**: 808–816.
70 Margolis DJ, Hoffstad O, Bilker W. Lack of association between exposure to topical calcineurin inhibitors and skin cancer in adults. *Dermatology* 2007; **214**: 289–295.
71 Reitamo S, Van Leent EJ, Ho V *et al.* Efficacy and safety of tacrolimus ointment compared with that of hydrocortisone acetate ointment in children with atopic dermatitis. *J Allergy Clin Immunol* 2002; **109**: 539–546.
72 Patel RR, Vander Straten MR, Korman NJ. The safety and efficacy of tacrolimus therapy in patients younger than 2 years with atopic dermatitis. *Arch Dermatol* 2003; **139**: 1184–1186.
73 Ho VC, Gupta A, Kaufmann R *et al.* Safety and efficacy of nonsteroid pimecrolimus cream 1% in the treatment of atopic dermatitis in infants. *J Pediatr* 2003; **142**: 155–162.
74 Eichenfield LF, Lucky AW, Boguniewicz M *et al.* Safety and efficacy of pimecrolimus (ASM 981) cream 1% in the treatment of mild and moderate atopic dermatitis in children and adolescents. *J Am Acad Dermatol* 2002; **46**: 495–504.
75 Reitamo S, Rustin M, Harper J *et al.* A 4-year follow-up study of atopic dermatitis therapy with 0.1% tacrolimus ointment in children and adult patients. *Br J Dermatol* 2008; **159**: 942–951.
76 Langley RG, Eichenfield LF, Lucky AW, Boguniewicz M, Barbier N, Cherill R. Sustained efficacy and safety of pimecrolimus cream 1% when used long-term (up to 26 weeks) to treat children with atopic dermatitis. *Pediatr Dermatol* 2008; **25**: 301–307.
77 Wollenberg A, Sidhu MK, Odeyemi I *et al.* Economic evaluation of secondary prophylactic treatment with tacrolimus 0.1% ointment in adults with moderate to severe atopic dermatitis. *Br J Dermatol* 2008; **159**: 1322–1330.
78 Diepgen TL. Long-term treatment with cetirizine of infants with atopic dermatitis: a multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatr Allergy Immunol* 2002; **13**: 278–286.
79 De Benedetto A, Agnihothri R, McGirt LY, Bankova LG, Beck LA. Atopic dermatitis: a disease caused by innate immune defects? *J Invest Dermatol* 2009; **129**: 14–30.
80 Lübbe J. Secondary infections in patients with atopic dermatitis. *Am J Clin Dermatol* 2003; **4**: 641–654.
81 Shah M, Mohanraj M. High levels of fusidic acid resistant *Staphylococcus aureus* in dermatology patients. *Br J Dermatol* 2003; **148**: 1018–1020.
82 Niebuhr M, Mai U, Kapp A, Werfel T. Antibiotic treatment of cutaneous infections with *Staphylococcus aureus* in patients with atopic dermatitis: current antimicrobial resistances and susceptibilities. *Exp Dermatol* 2008; **17**: 953–957.
83 Bunikowski R, Mielke M, Skarabis H *et al.* Evidence for a disease-promoting effect of staphylococcus aureus-derived exotoxins in atopic dermatitis. *J Allergy Clin Immunol* 2000; **105**: 814–819.
84 Zollner T, Wichelhaus T, Hartung A *et al.* Colonization with superantigen-producing *Staphylococcus aureus* is associated with increased severity of atopic dermatitis. *Clin Exp Allergy* 2000; **30**: 994–1000.
85 Hauser C, Wuethrich B, Matter L. *Staphylococcus aureus* skin colonization in atopic dermatitis. *Dermatol Helv* 1985; **170**: 35.
86 Breuer K, Haussler S, Kapp A, Werfel T. Staphylococcus aureus: colonizing features and influence of an antibacterial treatment in adults with atopidermatitis. *Br J Dermatol* 2002; **147**: 55–61.
87 Leyden J, Kligman A. The case for steroid-antibiotic combinations. *Br J Dermatol* 1977; **96**: 179–187.
88 Brockow K, Grabenhorst P, Abeck D *et al.* Effect of gentian violet, corticosteroid and tar preparations in Staphylococcus-aureus-colonized atopic eczema. *Dermatology* 1999; **199**: 231–236.
89 Lever R. Infection in atopic dermatitis. *Dermatol Ther* 1996; **1**: 32–37.
90 David T, Cambridge G. Bacterial infection and atopic eczema. *Arch Dis Child* 1986; **61**: 20–23.
91 Adachi J, Endo K, Fukuzumi T, Tanigawa N, Aoki T. Increasing incidence of streptococcal impetigo in atopic dermatitis. *J Dermatol Sci* 1998; **17**: 45–53.
92 Ewing C, Ashcroft C, Gibbs A. Flucloxacillin in the treatment of atopic dermatitis. *Br J Dermatol* 1998; **138**: 1022–1029.
93 Gauger A, Mempel M, Schekatz A, Schäfer T, Ring J, Abeck D. Silver-coated textiles reduce *Staphylococcus aureus* colonization in patients with atopic eczema. *Dermatology* 2003; **207**: 15–21.
94 Ricci G, Patrizi A, Bendandi B, Menna G, Varotti E, Masi M. Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. *Br J Dermatol* 2004; **150**: 127–131.
95 Lintu P, Savolainen J, Kortekangas-Savolainen O, Kalimo K. Systemic ketoconazole is an effective treatment of atopic dermatitis with IgE-mediated hypersensitivity to yeasts. *Allergy* 2001; **56**: 512–517.
96 Mayser P, Kupfer J, Nemetz D *et al.* Treatment of head and neck dermatitis with ciclopiroxolamine cream – results of a double-blind, placebo-controlled study. *Skin Pharmacol Physiol* 2006; **19**: 153–158.
97 Wollenberg A, Wetzel S, Burgdorf WHC, Haas J. Viral infections in atopic dermatitis: pathogenic aspects and clinical management. *J Allergy Clin Immunol* 2003; **112**: 667–674.
98 Wollenberg A, Zoch C, Wetzel S, Plewig G, Przybilla B. Predisposing factors and clinical features of eczema herpeticum – a retrospective analysis of 100 cases. *J Am Acad Dermatol* 2003; **49**: 198–205.
99 Stalder J, Fleury M, Sourisse M. Local steroid therapy and bacterial skin flora in atopic dermatitis. *Br J Dermatol* 1994; **131**: 536–540.
100 Syed TA, Goswami J, Ahmadpour OA, Ahmad SA. Treatment of molluscum contagiosum in males with an analog of imiquimod 1% in cream: a placebo-controlled, double-blind study. *J Dermatol* 1998; **25**: 309–313.
101 Gambichler T, Kreuter A, Tomi NS *et al.* Gene expression of cytokines in atopic eczema before and after ultraviolet A1 phototherapy. *Br J Dermatol* 2008; **158**: 1117–1120.
102 Dotterud LK, Wilsgaard T, Vorland LH *et al.* The effect of UVB radiation on skin microbiota in patients with atopic dermatitis and healthy controls. *Int J Circumpolar Health* 2008; **67**: 254–260.
103 Hong SP, Kim MJ, Jung MY *et al.* Biopositive effects of low-dose UVB on epidermis: coordinate upregulation of antimicrobial peptides and permeability barrier reinforcement. *J Invest Dermatol* 2008; **128**: 2880–2887.
104 Williams HC, Grindlay DJ. What's new in atopic eczema? An analysis of the clinical significance of systematic reviews on atopic eczema published in 2006 and 2007. *Clin Exp Dermatol* 2008; **33**: 685–688.

105 Gambichler T, Othlinghaus N, Tomi NS *et al.* Medium-dose ultraviolet (UV) A1 vs. narrowband UVB phototherapy in atopic eczema: a randomized crossover study. *Br J Dermatol* 2009; **160**: 652–658.
106 Majoie IM, Oldhoff JM, van Weelden H *et al.* Narrowband ultraviolet B and medium-dose ultraviolet A1 are equally effective in the treatment of moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2009; **60**: 77–84.
107 Chuang TY, Heinrich LA, Schultz MD, Reizner GT, Kumm RC, Cripps DJ. PUVA and skin cancer. A historical cohort study on 492 patients. *J Am Acad Dermatol* 1992; **26**: 173–177.
108 Mavilia L, Mori M, Rossi R *et al.* 308 nm monochromatic excimer light in dermatology: personal experience and review of the literature. *G Ital Dermatol Venereol* 2008; **143**: 329–337.
109 Akhavan A, Rudikoff D. Atopic dermatitis: systematic immunosuppressive therapy. *Semin Cutan Med Surg* 2008; **27**: 151–155.
110 Berth-Jones L, Finlay A, Zaki I *et al.* Ciclosporin in severe childhood atopic dermatitis: a multicentre study. *J Am Acad Dermatol* 1996; **34**: 1016–1021.
111 Van Joost T, Heule F, Korstanje M, Van-den-Broek M, Stenveld H, Van-Vloten W. Ciclosporin in atopic dermatitis: a multicentre, placebo-controlled study. *Br J Dermatol* 1994; **130**: 634–640.
112 Murphy LA, Atherton D. A retrospective evaluation of azathioprine in severe childhood atopic eczema, using thiopurine methyltransferase levels to exclude patients at high risk of myelosuppression. *Br J Dermatol* 2002; **147**: 308–315.
113 Berth-Jones J, Takwale A, Tan E *et al.* Azathioprine in severe adult atopic dermatitis: a double-blind, placebo-controlled, crossover trial. *Br J Dermatol* 2002; **147**: 324–330.
114 Grundmann-Kollmann M, Podda M, Ochsendorf F, Boehncke W-H, Kaufmann R, Zollner T. Mycophenolate mofetil is effective in the treatment of atopic dermatitis. *Arch Dermatol* 2001; **137**: 870–873.
115 Heller M, Shin HT, Orlow SJ, Schaffer JV. Mycophenolate mofetil for severe childhood atopic dermatitis: experience in 14 patients. *Br J Dermatol* 2007; **157**: 127–132.
116 Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol* 2007; **32**: 23–27.
117 Goujon C, Berard F, Dahel K *et al.* Methotrexate for the treatment of adult atopic dermatitis. *Eur J Dermatol* 2006; **16**: 155–158.
118 Simon D, Wittwer J, Kostylina G, Buettiker U, Simon HU, Yawalkar N. Alefacept (lymphocyte function-associated molecule 3/IgG fusion protein) treatment for atopic eczema. *J Allergy Clin Immunol* 2008; **122**: 423–424.
119 Moul DK, Routhouska SB, Robinson MR, Korman NJ. Alefacept for moderate to severe atopic dermatitis: a pilot study in adults. *J Am Acad Dermatol* 2008; **58**: 984–989.
120 Simon D, Hösli S, Kostylina G, Yawalkar N, Simon HU. Anti-CD20 (rituximab) treatment improves atopic eczema. *J Allergy Clin Immunol* 2008; **121**: 122–128.
121 Takiguchi R, Tofte S, Simpson B *et al.* Efalizumab for severe atopic dermatitis: a pilot study in adults. *J Am Acad Dermatol* 2007; **56**: 222–227.
122 Vigo PG, Girgis KR, Pfuetze BL, Critchlow ME, Fisher J, Hussain I. Efficacy of anti-IgE therapy in patients with atopic dermatitis. *J Am Acad Dermatol* 2006; **55**: 168–170.
123 Lane JE, Cheyney JM, Lane TN, Kent DE, Cohen DJ. Treatment of recalcitrant atopic dermatitis with omalizumab. *J Am Acad Dermatol* 2006; **54**: 68–72.
124 Sheinkopf LE, Rafi AW, Do LT, Katz RM, Klaustermeyer WB. Efficacy of omalizumab in the treatment of atopic dermatitis: a pilot study. *Allergy Asthma Proc* 2008; **29**: 530–537.
125 Krathen RA, Hsu S. Failure of omalizumab for treatment of severe adult atopic dermatitis. *J Am Acad Dermatol* 2005; **53**: 338–340.
126 Oldhoff JM, Darsow U, Werfel T *et al.* Anti-IL-5 recombinant humanized monoclonal antibody (mepolizumab) for the treatment of atopic dermatitis. *Allergy* 2005; **60**: 693–696.
127 Jacobi A, Antoni C, Manger B, Schuler G, Hertl M. Infliximab in the treatment of moderate to severe atopic dermatitis. *J Am Acad Dermatol* 2005; **52**: 522–526.
128 Isolauri E, Sütas Y, Kankaanpää P, Arvilommi H, Salminen S. Probiotics: effects on immunity. *Am J Clin Nutr* 2001; **73**: 444–450.
129 Grüber C, Wendt M, Sulser C *et al.* Randomized, placebo-controlled trial of *Lactobacillus rhamnosus* GG as treatment of atopic dermatitis in infancy. *Allergy* 2007; **62**: 1270–1276.
130 Fölster-Holst R, Müller F, Schnopp N *et al.* Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006; **155**: 1256–1261.
131 Lee J, Seto D, Bielory L. Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 2008; **121**: 116–121.
132 Kopp MV, Hennemuth I, Heinzmann A, Urbanek R. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of Lactobacillus GG supplementation. *Pediatrics* 2008; **121**: 850–856.
133 James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med* 1995; **332**: 1262–1266.
134 Staab D, Diepgen TL, Fartasch M *et al.* Age related, structured educational programmes for the management of atopic dermatitis in children and adolescents: multicentre, randomised controlled trial. *BMJ* 2006; **332**: 933–938.
135 Langan SM, Thomas KS, Williams HC. What is meant by a ''flare'' in atopic dermatitis? A systematic review and proposal. *Arch Dermatol* 2006; **142**: 1190–1196.

Appendix

O. Baadsgaard, Hellerup, Denmark; T. Bieber, Bonn, Germany; E. Bonifazi, Bari, Italy; C.A.F.M. Bruijnzeel-Koomen, Utrecht, The Netherlands; A. M. Calza, Geneva, Switzerland; M. Deleuran, Aarhus, Denmark; U. Darsow, Munich, Germany; J. De la Cuadra, Valencia, Spain; L. De Raeve, Brussels, Belgium; T.L. Diepgen, Heidelberg, Germany; P. Dupuy, Castanet Tolosan, France; G. Fabrizi, Rome, Italy; C. Gelmetti, Milan, Italy; A. Giannetti, Modena, Italy; U. Gieler, Gießen, Germany; F. Giusti, Modena, Italy; J. Harper, London, England; E.A. Holm, Copenhagen, Denmark; M. Kägi, Zürich, Switzerland; O. Kekki, Tampere, Finland; B. Kunz, Hamburg, Germany; R. Lever, Glasgow, Scotland; J. Lübbe, Geneva, Switzerland; A.B. Olesen, Aarhus, Denmark; A. P. Oranje, Rotterdam, The Netherlands; Y. de Prost, Paris, France; G. Rajka, Oslo, Norway; T. Reunala, Tampere, Finland; J. Revuz, Créteil, France; J. Ring, Munich, Germany; S. Seidenari, Modena, Italy; D. Simon, Bern, Switzerland; M. Song, Brussels, Belgium; J.F. Stalder, Nantes, France; A. Svensson, Malmö, Sweden; A. Taïeb, Bordeaux, France; D. Tennstedt, Brussels, Belgium; K. Turjanmaa, Tampere, Finland; C. Vestergaard, Aarhus, Denmark; T. Werfel, Hannover, Germany; A. Wollenberg, Munich, Germany