JEADV (2005) **19**, 286–295
DOI: 10.1111/j.1468-3083.2005.01249.x

POSITION PAPER

Position paper on diagnosis and treatment of atopic dermatitis

U Darsow,*† J Lübbe,‡ A Taïeb,§ S Seidenari,¶ A Wollenberg,†† AM Calza,‡ F Giusti,¶ J Ring,† for the European Task Force on Atopic Dermatitis[a]

*†Department of Dermatology and Allergy Biederstein, and Division of Environmental Dermatology and Allergy GSF/TUM, Technical University Munich, Germany, ‡Clinique de Dermatologie, Hôpital Cantonal Universitaire, Genève, Switzerland, §Service de Dermatologie, Hôpital St André, Bordeaux, France, ¶Department of Dermatology, University of Modena and Reggio Emilia, Italy, ††Department of Dermatology and Allergy, Ludwig-Maximilians-University Munich, Germany. *Corresponding author, Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Biedersteiner Str. 29, 80802 Munich, Germany, fax +49 89 4140 3171; E-mail: ulf.darsow@lrz.tum.de*

ABSTRACT

The diagnosis of atopic dermatitis (AD) is made using evaluated clinical criteria. Management of AD must consider the symptomatic variability of the disease. It is based on hydrating topical treatment, and avoidance of specific and unspecific provocation factors. Anti-inflammatory treatment is used for exacerbation management. Topical corticosteroids remain the first choice. Systemic anti-inflammatory treatment should be kept to a minimum, but may be necessary in rare refractory cases. The new topical calcineurin inhibitors (tacrolimus and pimecrolimus) expand the available choices of topical anti-inflammatory treatment. Microbial colonization and superinfection (e.g. with *Staphylococcus aureus*, *Malassezia furfur*) can have a role in disease exacerbation and can justify the use of antimicrobials in addition to the anti-inflammatory treatment. Evidence for the efficacy of systemic antihistamines in relieving pruritus is still insufficient, but some patients seem to benefit. Adjuvant therapy includes ultraviolet (UV) irradiation preferably of UVA wavelength; UVB 311 nm has also been used successfully. Dietary recommendations should be specific and only given in diagnosed individual food allergy. Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programmes have proved to be helpful.

Key words: atopic eczema/dermatitis, treatment, position paper, ETFAD

Received: 16 December 2004, accepted 5 January 2005

[a]D Abeck, Munich, Germany; O Baadsgaard, Hellerup, Denmark; T Bieber, Bonn, Germany; E Bonifazi, Bari, Italy; CAFM Bruijnzeel-Koomen, Utrecht, the Netherlands; AM Calza, Geneva, Switzerland; U Darsow, Munich, Germany; J De la Cuadra, Valencia, Spain; L De Raeve, Brussels, Belgium; TL 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, UK; M Kägi, Zürich, Switzerland; B Kunz, Hamburg, Germany; R Lever, Glasgow, Scotland, UK; J Lübbe, Geneva, Switzerland; AB Olesen, Aarhus, Denmark; AP 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; AM Schmitt, Toulouse, France; S Seidenari, Modena, Italy; D Simon, Bern, Switzerland; M Song, Brussels, Belgium; JF Stalder, Nantes, France; A Svensson, Malmö, Sweden; A Taïeb, Bordeaux, France; D Tennstedt, Brussels, Belgium; K Turjanmaa, Tampere, Finland; A Wollenberg, Munich, Germany.

© 2005 European Academy of Dermatology and Venereology

Introduction

Atopic dermatitis (AD, atopic eczema, eczema) is an inflammatory, chronically relapsing, non-contagious and intensely pruritic skin disease often occurring in families with other atopic diseases (bronchial asthma, allergic rhino-conjunctivitis). With a prevalence of 2–5% (in children and young adults around 15%), it 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' and 'endogenous eczema' are just a 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.[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]

In the first months of life, a yellowish desquamation on the scalp, known as 'cradlecap', 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 psoriasiform hyperplasia, spongiosis occasionally leading to vesicle formation, a marked inflammatory infiltrate composed of lymphocytes and monocytes, a variable number of eosinophils and mast cells in the upper dermis, and 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.[7]

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, 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, namely pruritus, typical morphology and distribution, chronic or chronically relapsing course, and atopic personal or family history, in addition to three minor criteria among a list of 21.[1] According to the UK working party[8] who developed criteria especially suitable for epidemiological purposes, but not in young children, itchy skin changes have to be diagnosed in the past 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 work-up must include a detailed inquiry on the circumstances of the flare, and a careful dermatological examination including lymph nodes, orifices and all skin folds. A professional attitude towards the exacerbated disease sets 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.

Basic therapy of AD 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 has been made by Hoare *et al.*[9] with regard to evidence-based therapies.[10–12] However, regimens for basic/maintenance therapy are still waiting for validation.

Cleaning

The skin must be cleansed thoroughly to remove crusts and eliminate mechanically bacterial contaminants in the case of bacterial superinfection. Cleansers with or without antiseptics (the duration of action of antiseptics is very limited, thus mechanical cleansing is probably more important) can be used, in non-irritant and low allergic formulas available in various galenic forms (syndets, aqueous solutions). In infants, it is easier to perform this first stage of gentle cleansing of the skin on the nappy changing mattress rather than directly in the bathtub. A further cleansing followed by a rapid rinse is performed in the bath (33–34 °C). The short duration of the bath and the use of bath oils is aimed to avoid epidermal dehydration. Topical emollients are preferentially applied directly after a bath or shower, when the skin is still slightly humid, after gentle drying.

Emollient therapy

AD is associated with skin barrier anomalies that lead to easier allergen penetration through the skin, and increased proneness to irritancy and subsequent cutaneous inflammation. A lack of important stratum corneum intercellular lipids and an inadequate ratio between compounds (cholesterol, essential fatty acids, ceramides) enhances transepidermal water loss leading to epidermal microfissuring that may also cause direct exposure of nerve endings. A better molecular and biochemical knowledge of this predisposing background should give access to barrier-improving topicals. Promising studies have recently been carried out along this line.[13] The cost of high-quality, allergy-safe emollient therapy products generally restricts their use because such products are considered as non-prescription drugs, and the quantities needed 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.

Hydration of the skin is usually maintained with at least twice daily application of moisturizers with a hydrophilic base, which may contain *ca.* 5% urea, if tolerated. Emulsions, or micellar solutions, as well as bath oils may also help to reduce the flares.

Educational programmes and counselling (Table 1)

Educational programmes and counselling, although time-consuming, are particularly important. 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 constraints. Early detection and prevention of bronchial asthma in infants with AD is part of the global management. Vaccinations, including those against measles in cases of hen's egg allergy, are safe,[14] the only restriction being the quality of skin care to avoid superinfection at injection sites.

Education programmes for patients and parents have been established recently in different European countries. Standardized interdisciplinary programmes involving dermatologists, paediatricians, psychologists/psychosomatic counsellors, and dietary counsellors may improve subjective and objective symptoms and optimize medication use in patients, and result in a significant increase in quality of life.

Table 1 List of aggravating factors and hygiene counselling for AD patients (adapted from Taïeb, in Saurat *et al.*[15])

- Clothing: avoid skin contact with irritating fibres (wool, large-fibre textiles); do not use tight and too warm clothing to avoid excessive sweating. New nonirritating clothing designed for AD children is currently being evaluated
- Tobacco: avoid exposure
- Cool temperature in the 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 at 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

  Maintain breastfeeding until 6 months if possible and delay introduction of solid foods until the seventh month. Avoid foods possibly containing peanut (marked 'vegetal fat')

  Otherwise normal diet, unless an allergy work-up 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 floors and upholstery once a week with an adequate filtered cleaner

  Avoid soft toys in bed (cot), except washable ones

  Wash bed sheets at a temperature higher than 55 °C every 10 days

  Bed and pillow encasings in GoreTex or similar

  Furred pets: advise to avoid preventively. If allergy is demonstrated, be firm on avoidance measures
- Pollen: Close windows during peak pollen season in warm and dry weather and restrict, if possible, stays outdoors. Aeration at night and early in the morning or in rainy weather. Avoid exposure to risk situations (lawn mowing). Pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen

Avoidance strategies on the basis of allergy diagnosis

AD is an inflammatory skin disorder with a relapsing course, associated with 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 eggs, wheat, soy and peanuts are most frequently responsible for eczema or exacerbation. When challenging AD patients with food, either early reactions are observed, such as urticaria, gastrointestinal or respiratory symptoms occurring within 120 min after the administration of the allergens, or late-phase responses occur, manifesting as eczematous lesions, occurring after 2–48 h or some days. Some patients show both immediate and delayed reactions after food intake. The personal history, especially in case of delayed reactions and when several foods are involved, is often not of great help in diagnosing food allergy. Immediate skin reactions to food can be investigated by means of different *in vivo* tests (skin prick tests, prick–prick tests, skin application food test, labial food challenge) and *in vitro* tests (serum specific IgE, histamine release, lymphocyte proliferation), whereas patch tests prove to be useful for studying delayed food-related skin responses.

In most cases *in vitro* tests do not add anything to the diagnostic capabilities of skin prick tests (SPTs), except in the case of dermographism or ultraviolet (UV)- and drug-induced skin hyporeactivity, when *in vivo* tests cannot be performed.

Atopy patch tests (APTs) are performed with self-made food material applied to the back with large test chambers for 48–72 h. Readings are performed according to European Task Force on Atopic Dermatitis (ETFAD) guidelines.[16] So far, APTs have been demonstrated to improve the accuracy of skin testing in the diagnosis of allergy to cow's milk, eggs, cereals and peanuts in AD patients.[17–23] Whereas immediate-type reactions are associated with SPT positivity, delayed reactions are related to positive responses to APTs. Combined prick and patch testing was found to enhance identification of food allergy in AD patients and to help in prescribing elimination diets. However, their results have to be correlated with food challenge.

The double-blind, placebo-controlled food challenge (DBPCFC) is considered to be the gold standard for diagnosing food allergy.[24] However, challenge tests based on repeated exposure to food (for 7 days) are more practical and enable the assessment of delayed adverse responses. Their results are comparable with those of DBPCFC.[17,18,22,23]

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 work-up of suspected allergy to aeroallergens includes *in vivo* and *in vitro* detection of specific IgE by means of SPTs or serological assays. However, both techniques have a low predictive value.

Patch testing AD patients with aeroallergens,[25] a procedure now known as the APT,[26] mentioned earlier, has been performed with house dust mites, pollen and animal dander, giving different positivity rates (15–100%) according to the patch test materials and modalities used.[19,26–29] Positive SPTs and/or high levels of specific IgE in serum are not a prerequisite for a positive APT response.[30] As regards the relevance of APTs, on the basis of the history of aeroallergen-triggered AD flares, APTs proved to have higher specificity and lower sensitivity than SPTs and specific IgE.

Although no gold standard for provocation of eczema in aeroallergen-mediated AD exists to date, in patients reacting to APTs specific avoidance strategies should be considered (Table 1).

Allergen-specific immunotherapy

The efficacy of specific immunotherapy in AD is difficult to prove by DBPC trials; however, this therapeutic procedure can be proposed in selected cases.[31]

Contact allergy

The role of contact allergy in AD patients is frequently underestimated.[32,33] 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 should be introduced from an early age 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, sodium laurylsulphate (SLS) pretreatment of nickel patch test sites was found to induce an earlier onset of the inflammatory reaction and 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.[34]

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 those of hairdressers, cleaners, metalworkers, mechanics and nurses, where hand eczema is a very common disease.[34] 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 two fundamental principles: sufficient dosage and correct application. Topical treatment should always be applied on hydrated skin, especially when using ointments. Patients, and children in particular, with acute, oozing and erosive lesions sometimes do not tolerate standard topical application, and may first be treated with 'wet wraps' until the oozing stops. Wet wraps are highly effective in acute eczema and improve tolerance.[35,36] 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.

Corticosteroids

Topical glucocorticosteroids are a first-line anti-inflammatory treatment, applied on inflammatory skin according to needs (pruritus, sleeplessness, new flare). With mild disease activity, a small amount of topical corticosteroids two to three times 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), along with the liberal use of emollients, generally achieves a good maintenance with SCORAD (Scoring of Atopic Dermatitis) values below 15–20. Such monthly amounts of even potent topical steroids do not usually have adverse systemic or local effects.

Topical corticosteroids are grouped by potency, which should be known to prescribers. Potent and very potent corticosteroids (groups 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 rapidly due to more rapid restitution of the skin barrier.[37,38] 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 of 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.[39,40] The most constructive way to spare steroids and avoid steroid-related side-effects is not to avoid 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.[41]

Topical calcineurin inhibitors

The two steroid-free topical calcineurin inhibitors, tacrolimus ointment and pimecrolimus cream, are useful new drugs for topical eczema treatment. Recent publications have reviewed various aspects of these drugs in detail.[42] The efficacy of both formulations has been demonstrated against placebo in clinical trials for their short-term[43,44] and long-term use.[45,46] The anti-inflammatory potency of 0.1% tacrolimus ointment is similar to a corticosteroid with intermediate activity,[47] while the latter is clearly more active than 1.0% pimecrolimus cream.[48]

Safety data for 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 burning at the application site.[43,48] It starts about 5 min after each application of the drug and may last up to one hour, but the intensity and duration typically decrease to zero within one week.[49] Generalized viral infections such as eczema herpeticum or eczema molluscatum have been observed during topical calcineurin inhibitor treatment.[50,51] It is unclear if a trend for increased frequency of viral superinfections exists, as only one controlled clinical trial has shown an increased frequency of eczema herpeticum,[52] whereas a large number of controlled clinical trials failed to do so.[53,54] In contrast to corticosteroids, none of the topical calcineurin inhibitors induces skin atrophy.[55,56] This favours their use over topical corticosteroids in delicate body areas such as the eyelid region, the perioral skin, the genital area or the inguinal fold, and for topical long-term management. Clinical and preclinical data do not indicate an increased risk of photocarcinogenicity for topical calcineurin inhibitors, but as the continuous oral administration of the calcineurin inhibitor cyclosporin is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection (e.g. with sunscreens) is advisable.[49] 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.[47,57] Fewer data

are available for children under 2 years of age.[58] Pimecrolimus cream has been studied in infants and children in a combination regimen with topical corticosteroids,[59,60] the latter being given if a flare occurred. Both topical calcineurin inhibitors are approved in the European Union from 2 years of age and above. The cost-effectiveness of a first-line treatment with topical calcineurin inhibitors awaits further studies.

Antihistamines

Systemic antihistamines (anti-H1) are widely used in acute flares against itch; however, there are few controlled studies.[61] 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 antihistamines, large controlled studies are missing to date. Topical antihistamines have no effect beyond that of their cooling vehicles.

Antibacterial therapy

The lack of inducible antimicrobial peptides in AD favours the recurrent cutaneous colonization with *Staphylococcus aureus*.[62] 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.[63,64] However, there is evidence for an association of *S. aureus*-derived superantigens with disease exacerbation,[65,66] supporting early observations that the density of *S. aureus* colonization in AD is significantly correlated with clinical severity,[67] and that patients with high numbers of colonizing *S. aureus* can benefit from combination treatment with corticosteroids and antibiotics.[68,69] As 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 a topical antibiotic.[70] Topical antiseptics such as triclosan, chlorhexidine or crystal violet 0.3% are frequently regarded as less controversial than topical antibiotics. Apart from specific indications such as overt secondary infection or the presence of beta-haemolytic streptococci,[71,72] there is no consensus on the usefulness of systemic antibiotic therapy in AD, and a randomized study has failed to show an advantage with regard to clinical improvement and sparing of steroids.[73]

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.[74,75] These new options are still under investigation.

Other secondary infections, such as yeasts, dermatophytes and streptococcal infections have also been implicated as disease factors in AD (for a review, see[63]). 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. However, there is no conclusive clinical evidence suggesting that patients with AD may benefit from specific anti-infectious treatment in the absence of clinical signs of infection.[63]

Antiviral therapy

Viral infections occur more frequently in AD patients than in normal individuals, with a tendency to disseminated, widespread disease. The latter are named after the causative virus such as eczema molluscatum, eczema vaccinatum or eczema herpeticum.[76] A disseminated, distinctly monomorphic eruption of dome-shaped vesicles, accompanied by fever, malaise and lymphadenopathy, is suggestive for eczema herpeticum (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 (fig. 1). 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.[77] The clinical diagnosis should be confirmed by polymerase chain reaction (PCR), electron microscopy, immunofluorescence tests or viral culture. The keystone of EH therapy is prompt systemic antiviral chemotherapy with i.v. aciclovir, but a number of alternative treatment modalities exist.[76]

AD patients may develop widespread eczema molluscatum (EM) with up to several hundred umbilicated, small, skin-coloured papules.[76] Although EM lesions resolve spontaneously, treatment speeds healing and prevents spreading by auto- and heteroinoculation. In addition to mild anti-inflammatory treatment,[78] limited numbers of lesions may be destroyed with a small curved forceps, removed by curettage, or destroyed by cryotherapy or carbon dioxide laser vaporization.[76] Topical application of imiquimod or other topical immunostimulatory

fig. 1 Small, punched-out erosive or ulcerative lesions within the eczema are a sign of superinfection with herpes simplex and may progress to eczema herpeticum.

Table 2 Treatment of atopic dermatitis

Phase	Therapy
Baseline	Educational programmes, emollients, bath oils, elimination diet (in food-allergic patients), allergen avoidance (encasings, if diagnosed by allergy tests)
1 Mild (SCORAD ≤ 15)/transient	First line: topical glucocorticosteroids. Second line: topical calcineurin inhibitors, antiseptics, non-sedating antihistamines (controversial)
2 Moderate (SCORAD 15–40)/recurrent	Sedating antihistamines (doxepin, hydroxyzine), UV-therapy (UVB 311 nm, UVA1), psychosomatic counselling, climate therapy
3 Severe (SCORAD ≥ 40)/persistent	Hospitalization, systemic immunosuppression: oral glucocorticosteroids, azathioprin, cyclosporin A, oral tacrolimus, PUVA

For every phase, additional therapeutic options are given. Consider compliance, if therapy has no effect. Antiseptics/antibiotics in cases of superinfection.

drugs shows promising results,[79] but is expensive and not always well tolerated.

UV therapy

Both UVB and UVA therapies have been described in the treatment of AD. Broadband UVB, selective UV phototherapy (SUP), broadband UVB combined with low-dose UVA (2–10 J/cm^2) and also narrow-band UVB (311 nm) have been used. In addition, combinations of UVB and topical steroid and UVB with UVA showed favourable results, as well as UVA-1 medium- and high-dose regimens.[80,81] The efficacy of phototherapy is limited by erythema and inflammation. An optimal relationship of erythematous and anti-inflammatory effects seems to exist around 311 nm. Suberythematogenous UV doses with careful dose increments are often able to prevent exacerbations of AD; 24 h after irradiation a mild erythema may be seen. If narrow-band UVB therapy is performed 2–4 times a week, AD is often controlled after 6 weeks of treatment. Maintenance therapy can be reduced to 1–2 treatments per week. However, the long-term side-effects of narrow-band UVB are still unknown. Phototherapy is mostly a therapy for adolescents and adults but may be started earlier in refractory cases.

Systemic anti-inflammatory therapy

Resistance to well-conducted topical therapy is rare, and systemic anti-inflammatory treatment should be limited to the rare cases where the potential of topical treatment (or of patient compliance) has been exhausted. Systemic therapy increases medical dependence and reduces patient autonomy, which will be a handicap whenever attempts are made to switch back to topical management. Systemic therapy is not a rescue treatment for acute exacerbation but a reserve option for persistent, refractory disease. Corticosteroids are rapidly effective, but should be avoided as side-effects are inevitable in the long term. The usefulness of both cyclosporin (3–5 mg/kg/day) and azathioprine (2.5 mg/kg/day) has been well documented in clinical trials with children and adults.[82–85] Cyclosporin A therapy is rapidly effective, but has a narrow therapeutic index and requires a close follow-up for signs of renal impairment. Azathioprine has a slower onset of action and is not always well tolerated. Low thiopurine-methyltransferase (TPMT) activity is associated with an increased myelotoxicity of azathioprine, but patients at risk can be identified by pretreatment screening for TMTP activity.[84] Mycophenolate mofetil (2 g/day) seems to offer a more favourable security profile; its usefulness in severe AD remains to be assessed in larger randomized trials.[86]

References

1 Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol (Stockh)* 1980; **92**(Suppl.): 44–47.

2 Ruzicka T, Ring J, Przybilla B, eds. *Handbook of Atopic Eczema*. Springer, Heidelberg, 2005.

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 Immunol* 2002; **2**: 383–387.

7 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.

8 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.

9 Hoare C, Li Wan Po A, Williams H. Systematic review of treatments for atopic eczema. *Health Technol Assess* 2000; **4**: 1–191.

10 Thomas KS, Armstrong S, Avery A *et al.* Randomised controlled trial of short bursts of a potent topical corticosteroid versus prolonged use of a mild preparation for children with mild or moderate atopic eczema. *Br Med J* 2002; **324**: 768.

11 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.

12 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. *Br Med J* 2003; **326**: 1367.

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 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.

15 Saurat JH, ed. *Précis de Dermatologie*, 4th edn. Masson, Paris, 2004.

16 Kerschenlohr K, Darsow U, Burgdorf WHC *et al.* Lessons from atopy patch testing in atopic dermatitis. *Curr Allergy Asthma Rep* 2004; **4**: 285–289.

17 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.

18 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.

19 Darsow U, Ring J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000; **25**: 544–551.

20 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.

21 Roehr CC, Reibel S, Ziegert M *et al.* 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.

22 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.

23 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.

24 Bindslev-Jensen C. Standardization of double-blind, placebo-controlled food challenges. *Allergy* 2001; **56**: 75–77.

25 Mitchell EB, Crow J, Chapman MD *et al.* Basophils in allergen-induced patch test sites in atopic dermatitis. *Lancet* 1982; **1**: 127–130.

26 Ring J, Kunz B, Bieber T *et al.* The 'atopy patch test' with aeroallergens in atopic eczema. *J Allergy Clin Immunol* 1989; **82**: 195.

27 Seidenari S, Manzini BM, Danese P. Patch testing with pollen in patients with atopic dermatitis and mucosal atopy. *Contact Dermatitis* 1992; **27**: 25.

28 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.

29 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.

30 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.

31 Glover MT, Atherton DJ. A double-blind controlled trial of hyposensitization to *Dermatophagoides pteronyssinus* in children with atopic eczema. *Clin Exp Allergy* 1992; **22**: 440–446.

32 Manzini BM, Ferdani G, Simonetti V *et al.* Contact sensitization in children. *Contact Dermatitis* 1998; **15**: 12–17.

33 Mortz CG, Andersen KE. Allergic contact dermatitis in children and adolescents. *Contact Dermatitis* 1999; **41**: 121–130.

34 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, in press.

35 Goodyear H, Spowart K, Harper J. 'Wet-wrap' dressings for the treatment of atopic eczema in children. *Br J Dermatol* 1991; **125**: 604.

36 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.

37 Feiwel M, Munro D, James V. Effect of topically applied 0.1% betamethasone valerate ointment on the adrenal function of children. In: *Thirteenth Congress of International Dermatology*. Springer, Berlin, 1968: 202–204.

38 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.

39 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.

40 Charman C, Williams H. The use of corticosteroids and corticosteroid phobia in atopic dermatitis. *Clin Dermatol* 2003; **21**: 193–200.

41 Eichenfield L, Hanifin J, Beck L *et al.* Atopic dermatitis and asthma: parallels in the evolution of treatment. *Pediatrics* 2003; **111**: 608–616.

42 Bornhövd E, Burgdorf WHC, Wollenberg A. Macrolactam immunomodulators for topical treatment of inflammatory skin diseases. *J Am Acad Dermatol* 2001; **45**: 736–743.

43 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.

44 Van Leent EJ, Graber M, Thurston M *et al.* Effectiveness of the ascomycin macrolactam SDZ ASM 981 in the topical treatment of atopic dermatitis. *Arch Dermatol* 1998; **134**: 805–809.
45 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.
46 Meurer M, Fölster-Holst R, Wozel G *et al.* Pimecrolimus cream in the long-term management of atopic dermatitis in adults: a six-month study. *Dermatology* 2002; **205**: 271–277.
47 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.
48 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.
49 Bornhövd EC, Burgdorf WHC, Wollenberg A. Immunomodulatory macrolactams for topical treatment of inflammatory skin diseases. *Curr Opin Invest Drugs* 2002; **3**: 708–712.
50 Lübbe J, Pournaras CC, Saurat JH. Eczema herpeticum during treatment of atopic dermatitis with 0.1% tacrolimus ointment. *Dermatology* 2000; **201**: 249–251.
51 Wetzel S, Wollenberg A. Eczema molluscatum in tacrolimus treated atopic dermatitis. *Eur J Dermatol* 2004; **14**: 73–74.
52 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.
53 Lübbe J. Clinical experience with topical calcineurin inhibitors. *Hautarzt* 2003; **54**: 432–439.
54 Bornhövd E, Wollenberg A. Topical immunomodulators for the treatment of eczema. *Allergo J* 2003; **12**: 456–462.
55 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.
56 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.
57 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.
58 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.
59 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.
60 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.
61 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.
62 Ong PY, Ohtake T, Brandt C *et al.* Endogenous antimicrobial peptides and skin infections in atopic dermatitis. *N Engl J Med* 2002; **347**: 1151–1160.
63 Lübbe J. Secondary infections in patients with atopic dermatitis. *Am J Clin Dermatol* 2003; **4**: 641–654.
64 Shah M, Mohanraj M. High levels of fusidic acid resistant *Staphylococcus aureus* in dermatology patients. *Br J Dermatol* 2003; **148**: 1018–1020.
65 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.
66 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.
67 Hauser C, Wuethrich B, Matter L. *Staphylococcus aureus* skin colonization in atopic dermatitis patients. *Dermatologica* 1985; **170**: 35.
68 Leyden J, Kligman A. The case for steroid–antibiotic combinations. *Br J Dermatol* 1977; **96**: 179–187.
69 Lever R, Hadley K, Downey D, Mackie R. Staphylococcal colonization in atopic dermatitis and the effect of topical mupirocin therapy. *Br J Dermatol* 1988; **119**: 189–198.
70 Lever R. Infection in atopic dermatitis. *Dermatol Ther* 1996; **1**: 32–37.
71 David T, Cambridge G. Bacterial infection and atopic eczema. *Arch Dis Child* 1986; **61**: 20–23.
72 Adachi J, Endo K, Fukuzumi T *et al.* Increasing incidence of streptococcal impetigo in atopic dermatitis. *J Dermatol Sci* 1998; **17**: 45–53.
73 Ewing C, Ashcroft C, Gibbs A. Flucloxacillin in the treatment of atopic dermatitis. *Br J Dermatol* 1998; **138**: 1022–1029.
74 Gauger A, Mempel M, Schekatz A *et al.* Silver-coated textiles reduce *Staphylococcus aureus* colonization in patients with atopic eczema. *Dermatology* 2003; **207**: 15–21.
75 Ricci G, Patrizi A, Bendandi B *et al.* Clinical effectiveness of a silk fabric in the treatment of atopic dermatitis. *Br J Dermatol* 2004; **150**: 127–131.
76 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.
77 Wollenberg A, Zoch C, Wetzel S *et al.* Predisposing factors and clinical features of eczema herpeticum – a retrospective analysis of 100 cases. *J Am Acad Dermatol* 2003; **49**: 198–205.
78 Stalder J, Fleury M, Sourisse M. Local steroid therapy and bacterial skin flora in atopic dermatitis. *Br J Dermatol* 1994; **131**: 536–540.
79 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.

80 Abeck D, Schmidt T, Fesq H *et al.* Long-term efficacy of medium-dose UVA1 phototherapy in atopic dermatitis. *J Am Acad Dermatol* 2000; **42**: 254–257.

81 Reynolds NJ, Franklin V, Gray JC *et al.* Narrow-band ultraviolet B and broad-band ultraviolet A phototherapy in adult atopic eczema: a randomised controlled trial. *Lancet* 2001; **357**: 2012–2016.

82 Berth-Jones L, Finlay A, Zaki I *et al.* Cyclosporin in severe childhood atopic dermatitis: a multicentre study. *J Am Acad Dermatol* 1996; **34**: 1016–1021.

83 Van Joost T, Heule F, Korstanje M *et al.* Cyclosporin in atopic dermatitis: a multicentre, placebo-controlled study. *Br J Dermatol* 1994; **130**: 634–640.

84 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.

85 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.

86 Grundmann-Kollmann M, Podda M, Ochsendorf F *et al.* Mycophenolate mofetil is effective in the treatment of ato pic dermatitis. *Arch Dermatol* 2001; **137**: 870–873.