CONTINUING MEDICAL EDUCATION

The Diagnosis and Graded Therapy of Atopic Dermatitis

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SUMMARY

Background: Atopic dermatitis is the most common skin disease in children, with a prevalence of 10% to 15%, and is common in adults as well. Close coordination between primary care physicians and specialists is essential for the adequate treatment of chronically and severely affected patients.

Methods: This article is a review of pertinent publications that were retrieved by a selective search in Pubmed, with additional consideration of the guidelines of the Association of Medical Scientific Societies in Germany (AWMF) and the European Dermatology Forum.

Results: Trigger factors such as skin irritants, allergens, microbial pathogens, and psychological factors can affect the condition of the skin differently in individual patients and should be individually assessed. The use of skin moisturising creams or *emollients* along with avoidance of specific and unspecific irritants is of great importance, as these patients have an impaired cutaneous barrier. Topical anti-inflammatory treatment with glucocorticoids or calcineurin inhibitors is a central part of the management of atopic dermatitis; in exceptional cases, severely affected patients are treated with systemic anti-inflammatory drugs. Interdisciplinary patient education has been found to be an effective tool in the complex management of this disease. Chronically and severely affected patients present special challenges for diagnosis and treatment.

Conclusion: Recent advances in the understanding of the molecular basis of cutaneous barrier disorders and of congenital and acquired immune disorders have led to new approaches to the treatment of atopic dermatitis.

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Atopic dermatitis (atopic eczema) is the most common skin disease in children with a prevalence of 10–15% before school age. About half of the patients suffer from moderate to severe atopic dermatitis (1). Spontaneous healing can occur at any time but 1–2% of adults are also affected. The disease is of great economic importance because it is so common and generally chronic (2, e1). Frequently, the dermatitis is associated with other atopic diseases such as food allergies, asthma, and allergic rhinitis. The prevalence of food allergies in patients with severe atopic dermatitis is believed to be around 30% (3).

Learning objectives

After reading this article, the reader should be able to

- identify the most important trigger factors for atopic dermatitis, along with the appropriate diagnostic and therapeutic measures to address them.
- understand the role of allergens and the need for a stepwise diagnostic approach, and
- be familiar with the latest recommendations for topical and systemic therapy.

Clinical features of atopic dermatitis

The clinical features of atopic dermatitis vary depending on the stage (acute or chronic) of the disease and the age of the patients (*Table 1*). The most disabling feature is generally the chronic or chronic-recurrent pruritus; another significant cause of suffering is the associated social stigmatization. The course of the disease is highly variable with flares of varying severity and duration (4). Even what appears to be mild manifestations can greatly disturb the patient and cause emotional stress. Patients with atopic dermatitis are significantly more often depressed or anxious than healthy control groups, which may be a result of their suffering (5). Infections are a common complication of atopic

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Prevalence

Atopic dermatitis (atopic eczema) is the most common skin disease in childhood with a prevalence of 10–15% at the time of school entry.

TABLE 1

Characteristic age-dependent features of atopic dermatitis

< 2 years	> 2 years
Infants: Even with generalized disease, the diaper area is usually spared.	Children, adolescents and adults: Flexural dermatitis (antecubital and popliteal fossae)
Infants: Weeping scalp dermatitis (with white-gray crusts = cradle cap)	Adolescents and adults: Hand dermatitis, depending on skin irritant exposure
Infants and small children: Localized disease often confined to cheeks and extensor surfaces of limbs	Adults: Prurigo variant with very pruritic papules and nodules especially on the shoulder girdle and arms
Minimal variants of atopic dermatitis (all age groups): Cheilitis, perlèche, ear lobe fissures	

dermatitis and can be quite severe (*Figures 1 and 2, Box 1*).

Etiology, pathophysiology and prevention

Both genetic predisposition (skin barrier defects as well as impaired innate and acquired immunity) and trigger factors play important roles in both the onset of atopic dermatitis and the exacerbations (4, 6). Filaggrin loss-of-function mutations have received special attention in recent years (7). Filaggrin is a structural protein in differentiated keratinocytes. Loss-of-function mutations in filaggrin lead to skin barrier defects, reduced bacterial defenses, and an increased skin pH value. Filaggrin mutations are associated with an increased risk to develop atopic dermatitis (Odds Ratio 3.1–4.8) (7). About 25% of patients with atopic dermatitis have such mutations. Moreover, these patients are at increased risk of developing allergies and asthma, as well as eczema herpeticum, which is known to be a severe complication of atopic dermatitis.

The decreased incidence of infections in early childhood led to the so-called ‘hygiene hypothesis’ by David Strachan, which has been implicated in recent decades with the increased prevalence of atopic dermatitis (4–8-fold increase, depending on study); the same trend has been seen in other atopic disorders (4).

The clinical picture of dermatitis (cutaneous inflammation with epidermal involvement) results from the presence of T cells, IgE-binding antigen-presenting dendritic cells and eosinophils (8).

In the acute and subacute stages, a variety of mediators, especially the TH2 cytokines such as interleukin 4 (IL-4) and interleukin 13 (IL-13), are responsible for

the transient down-regulation of barrier proteins, even in the absence of loss-of-function filaggrin mutations (9).

The German AWMF S3 guidelines No. 61–13 on allergy prevention (Allergieprävention) give the current recommendations for dietary and preventive measures for high-risk families. The recommendations include 4 months of breast feeding (or the use of extensive protein hydrolysate formulas) and the early introduction of fish in the child’s diet. According to the 2009 version of the same German guidelines, age-appropriate solid foods should be started during the first year even in children at high risk for allergies (10).

Diagnosis and trigger factors

The diagnosis is usually made clinically. Both a detailed history with special attention paid to personal and family history of atopic disorders and a complete physical exam are required.

A skin biopsy is generally not needed if the history and clinical features are typical, but may be useful for differential diagnostic purposes on occasion (11). The most common differential diagnostic considerations, including other forms of dermatitis such as allergic or irritant contact dermatitis, nummular dermatitis, and in adults an early stage of cutaneous T-cell lymphoma usually cannot be excluded microscopically. Hand dermatitis may often reflect a mixed picture of atopic, irritant and allergic contact dermatitis; it is generally difficult to classify precisely on the basis of etiology. When atopic dermatitis affects the hands and feet, both palmoplantar psoriasis and dermatophyte infections must be excluded. Less commonly one may encounter

Common complications

Infections are the most common complication of atopic dermatitis and can be quite severe.

Recommendations for prevention

- Nursing for 4 months or the use of extensive protein hydrolysate formulas
- Early introduction of fish into diet
- Introduction of solid foods in first year, also for children at risk for allergies.

syndromes or immunodeficiencies which can resemble atopic-dermatitis-like changes (*Box 2*). Several other inflammatory (also infectious) diseases of the skin, such as scabies in childhood, can occasionally be confused with atopic dermatitis.

When atopic dermatitis is suspected, it is necessary to be aware of possible psychosomatic factors, as well as dietary or environmental trigger factors. The importance of trigger factors varies greatly among individuals, but their identification and then avoidance or reduction are a key part of an individualized treatment approach. One must also be aware of the decreased sensitivity threshold for unspecific skin irritation due to the impaired barrier function.

Both infections and immunizations can cause exacerbations of atopic dermatitis. Nonetheless, according to the Standing Committee on Vaccination Recommendations (STIKO), both children and adults with atopic dermatitis should be immunized following the formal recommendations. In case of acute exacerbations, vaccinations should be avoided until the skin stabilizes (German AWMF S2 guideline 013–027 on atopic dermatitis [Neurodermitis]).

Allergy diagnostics in atopic dermatitis

Allergies in atopic dermatitis may not only present as a independent co-morbidity, but also influence the clinical picture of the underlying disease. Therefore it is important to individually assess the impact of potentially allergic reactions for the severity and clinical course of atopic dermatitis (*Box 3*). About 80% of patients are sensitized through IgE to common food or inhalational (pollen, animal hairs, house dust mites, molds) allergens. Even children who during the first years of life are diagnosed as having the less common non-allergic or intrinsic form of atopic dermatitis may later develop IgE antibodies (12). The determination of specific IgG levels has no diagnostic relevance in patients with suspected allergies and should not be employed. Measuring specific IgE antibodies against autoantibodies, which can be found in a subgroup of patients (13), is currently not a part of the routine diagnostic approach.

Allergy testing is indicated in patients who give a history of an immediate reaction (urticaria, rhinitis, bronchospasm within minutes) or a delayed onset or flare of dermatitis following allergen exposure.

IgE antibodies against animal hair allergens, especially from fur-bearing pets such as cats and various

Figure 1:
Skin infections in atopic dermatitis.
a) Mollusca contagiosa;
b) Eczema herpeticum

rodents, are most likely associated with acute respiratory reactions when they are clinically relevant. In this setting, one must seriously consider getting rid of the pets. In patients with chronic atopic dermatitis and proven sensitization to house dust mites, both special mattress covers and regular washing of pillows and bed covers are recommended (e2–e4).

In case of a suspected food allergy as a causing factor for delayed skin reactions, the patients history is of limited value as—in contrast to immediate-type reactions—the temporal relationship is uncertain (14). Searching for sensitization to food (especially in children) and inhalational allergens is recommended in patients with a severe chronic course, even in the absence of a history implicating these factors (15). Nevertheless, it is important to note that sensitization alone does not justify allergen avoidance or starting therapy; an elimination diet is only indicated in case of a clinically relevant immediate-type food allergy or if a delayed-type reaction is identified (14, 15, e5) (*Box 4*).

There is no evidence for a benefit of dietary restrictions without confirmed food allergies (16). Moreover,

Trigger factors

The importance of trigger factors varies greatly from individual to individual; identification of these factors and then their avoidance is part of an individualized therapy plan.

Infections and immunizations

Children and adults with atopic dermatitis should receive the routine immunizations. If the skin is acutely exacerbated, the immunization should be delayed until the skin findings have stabilized.

Figure 2:

Clinical features.

- a) Lichenified flexural dermatitis; left ante-cubital fossa is excoriated; right is moist and weeping;
- b) Dermatitis of nape in adult;
- c) Chronic eyelid dermatitis.

in children they carry the risks of severe malnutrition. Recent data indicates that non-immunologic reactions to food (“pseudo-allergies”) such as reactions to food additives or sugar play no role in atopic dermatitis; occasionally the ingestion of excessive amounts of citrus fruits has been implicated in worsening skin disease.

Patch testing with contact allergens may help to uncover the presence of an additional allergic contact dermatitis in a patient with chronic or therapy-resistant atopic dermatitis. Components of creams and ointments that are likely sensitizers (such as wool wax alcohols, cetyl stearyl alcohol, methylisothiazolinone, fragrances) are somewhat more likely to cause reactions in patients with atopic dermatitis than in healthy controls without the disorder. In contrast, the prevalence of nickel allergy is roughly equal in patients and controls (17, 18). The atopy patch test is an epicutaneous test that employs protein allergens (food, pollen or house dust mite) (19). Even though the positive test reactions are more clinically similar to atopic dermatitis than positive prick test reactions, it has not been incorporated into routine diagnostic recommendations because of the lack of approved standardized test materials.

Both the severity of the cutaneous disease as well as the involvement of special sites such as the hands can lead to significant impairment of patients' professional

life. Patients with atopic dermatitis should avoid working in a wet environment, very dirty conditions, frequent hand washing and repeated exposure to irritants. Health care workers who are required to frequently disinfect their hands or regularly wear protective gloves may experience a worsening of their atopic hand dermatitis. An individualized plan for skin protection as well as appropriately stage-adjusted therapy are required; occupational counseling should be offered to patients with clinically significant atopic dermatitis. Patients with occupationally induced or exacerbated hand dermatitis should be referred for evaluation to a dermatologist (cf. § 3 BeKV, German Social Accident Insurance), to initiate the appropriate treatment and, if applicable, preventive measures.

Topical therapy of atopic dermatitis

Treatment of atopic dermatitis basically focuses on symptomatic relief. The German AWMF guideline 013–027 on atopic dermatitis (Neurodermitis) and the graded therapy modified from the current European atopic dermatitis guidelines (20–22) (Figure 3) provide a framework for a therapeutic approach which must be modified depending on the patient's age, course, localization, and emotional stress.

Basic skin care in atopic dermatitis consists of reducing triggering factors by daily use of skin moisturising creams or emollients, as well as employing

Elimination diets

There is no evidence that non-individualized elimination diets are helpful. In children they carry the risk of malnutrition and retarded development.

Food allergies

Non-immunologic reactions to food additives or sugar play no role in atopic dermatitis. Ingestion of large amounts of citrus fruits is sometimes associated with a worsening of the skin condition.

stage-adjusted basic therapy. Newer knowledge of the molecular aspects of the disturbed barrier function has confirmed the crucial role of appropriate skin care. Controlled studies have demonstrated that applying moisturizers daily can lead to a reduced use of glucocorticosteroids (20). Inappropriate skin care measures can have local side effects such as exacerbating already dry or weeping areas through an improperly chosen vehicle. Every efforts should be made to insure that skin care products do not include any topical allergens.

Either urea (not in infants) or glycerine can be added to the maintenance vehicle. Urea binds to water and slows its loss from the epidermis, and up-regulates structural proteins and antimicrobial peptides (e6). When the skin is inflamed or in small children, the tolerability, especially of urea, should be assessed on a test area (e7).

Topical glucocorticosteroids are among the most important anti-inflammatory agents used in atopic dermatitis. They should be selected based on their potency which should be adjusted for the severity of the inflammation. If the therapeutic effect is insufficient, the dose can be increased. Topical glucocorticosteroids are usually employed once daily, but in exceptional cases can be used twice daily for short intervals (e8). Usually it is sufficient to use Class 1 glucocorticosteroids (weak, for example hydrocortisone or hydrocortisone acetate) in infants and Class 2 (moderate, for example prednicarbate, hydrocortisone butyrate) in older children and adults. The indications for strong or very strong glucocorticosteroids (Class 3 or rarely Class 4) are the short-term treatment of acute severe flares or therapy-resistant lichenified areas, as well as exacerbated palmoplantar dermatitis in adolescents and adults. Combined use with wet compress can enhance the effectiveness of topical glucocorticosteroids (23) but this approach should only be employed for short periods. Controlled studies with fluticasone propionate and methylprednisolone aceponate have shown that after healing, interval therapy with topical glucocorticosteroids (twice weekly; also known as proactive therapy) for several months can reduce the risk of recurrence and the total amount of glucocorticosteroids required without increasing the risk of local side effects (such as skin atrophy) (24, e9–e12).

This therapeutic approach is also effective with topical calcineurin inhibitors. Tacrolimus is approved for up to one year of proactive therapy after initial clearing (24, e13, e14).

Basic skin care

Basic skin care for atopic dermatitis consists of reducing or avoiding trigger factors and regular use of the appropriate emollients.

BOX 1

Therapeutic options for skin infections

- **Bacterial infections (usually Staphylococci)**
 - topical antiseptic agents, also in baths and clothing (for example, octenidine, triclosan, chlorhexidine as topical agents; silver in topical agents or textiles; diluted potassium permanganate or sodium hypochlorite in baths); systemic antibiotics for widespread clinical involvement
- **Viral infections: Mollusca contagiosa, severe verrucae vulgares, eczema herpeticum**
 - mechanical (curettage) or chemical destruction (mollusca or verrucae); systemic acyclovir, valacyclovir (eczema herpeticum)
- **Fungal infections: Dermatophytes (tinea), Malassezia species (most likely important in the head-neck-shoulder variant of atopic dermatitis)**
 - anti-mycotic agents (for example, ciclopirox olamine, imidazoles; usually topical)

Problem areas for treatment with topical glucocorticosteroids are the face, intertriginous areas and scrotum, as well as the scalp in children because of increased absorption. In these areas, only Class 1 or 2 glucocorticosteroids should be employed and just for a few days.

Regular daily treatment with sufficiently potent topical glucocorticosteroids can clear most lesions in most patients. A lack of response is often explained by non-adherence because of fear of glucocorticosteroids (25). Other explanations for a poor response are an allergic contact dermatitis to the corticosteroid itself, or a continued provocation of the atopic dermatitis by trigger factors. In addition there is a small group (less than 1%) of patients who do not respond sufficiently to glucocorticosteroids (non-responders).

Topical calcineurin inhibitors (pimecrolimus and tacrolimus) have been approved since 2002 for anti-inflammatory therapy in atopic dermatitis. Even with prolonged use, they do not lead to skin atrophy and do

Topical glucocorticosteroids

Topical glucocorticosteroids are among the most important anti-inflammatory substances used in atopic dermatitis. The choice of agent should be adjusted to the severity of the skin disease.

BOX 2

Immunodeficiency syndromes in differential diagnosis of atopic dermatitis

- Hyper IgE syndrome: 1) autosomal dominant hyper IgE syndrome (STAT3 defect) and 2) autosomal recessive hyper IgE syndrome (DOCK8 defect)
- Wiskott-Aldrich syndrome
- Omenn syndrome
- Netherton syndrome

Autosomal dominant hyper IgE with its typical findings of infections and bone involvement can usually be separated clinically from atopic dermatitis with elevated IgE levels, but skin disease in the other syndromes, especially in infants and children, may initially mimic atopic dermatitis (39, e27)

BOX 3

Indications for allergy testing (specific IgE, prick testing) in atopic dermatitis

- History of immediate allergic reaction or development of dermatitis after allergen exposure
- Severe chronic disease without history suggesting allergic component: evaluate for sensitization to foods (especially in children who have just started eating solid foods) and inhalational allergens
- Suggested screening panel for food allergies in children: cow milk, chicken eggs, soybeans, wheat, peanuts, hazelnuts, fish

not cause the facial side effects so common with glucocorticosteroids (steroid-induced rosacea, perioral dermatitis) (20, 21).

In all studies, topical calcineurin inhibitors have proven clearly better than placebo both for adults and children (2, 20, e1). Comparative trials indicate that topical calcineurin inhibitors are as effective as moderately effective glucocorticosteroids (e15–e17). Therapy with topical calcineurin inhibitors makes it possible to reduce the use of topical glucocorticosteroids; in addition, they do not lose effectiveness even when employed over a long period of time.

The most common side effect is a transient feeling of warmth or burning. Topical calcineurin inhibitors do not increase the risk of bacterial infections but the risk of viral infections such as herpes simplex virus is slightly elevated at 10–20% (22).

The European Medicines Agency (EMA) in a position paper on 27 March 2006 warned that the available data did not allow them to exclude an increased risk of cancer following use of topical calcineurin inhibitors and concluded that this risk should be weighed against the benefits when treating atopic dermatitis. In individual cases, physicians have reported an association of cancers during or following therapy with the topical calcineurin inhibitors tacrolimus and pimecrolimus, but such reports are so uncommon that they probably reflect two independent coincidental events. Eleven years after the approval of topical calcineurin inhibitors, there still are no registry-based reports or longitudinal studies showing an association between the use of these agents and skin cancer or lymphoma (26–28, e19–e21). There is also no evidence that they cause phototoxic or photoallergic reactions in humans. The recommendation to nonetheless employ effective photoprotection when using topical calcineurin inhibitors reflects generally accepted skin protection measures.

The affected skin in atopic dermatitis is, depending on severity, colonized in 50–90% of cases with *Staphylococcus aureus*; in normal controls, the rate is only 5–10% (29). Mild to moderate atopic dermatitis that responds well to topical glucocorticosteroids or calcineurin inhibitors generally does not require additional antibiotic therapy, as the number of bacteria decreases as the skin findings improve (e22). Patches of dermatitis which appear to be clinically superinfected can be treated with topical antiseptic drugs. Topical antibiotics should not be employed because of the risks of inducing resistant bacterial strains and causing allergic contact dermatitis.

Problem areas for employing topical glucocorticosteroids

- Face
- Intertriginous areas
- Scrotum
- Scalp in children

Topical calcineurin inhibitors

Topical calcineurin inhibitors are effective in treating atopic dermatitis and cause no skin atrophy. Their use is especially appropriate on sensitive sites like the face or intertriginous areas.

In addition to *S. aureus*, normally saprophytic *Malassezia* species may be increased in the variant of atopic dermatitis known as head-neck-shoulder dermatitis. Such patients with persistent or resistant disease may benefit from systemic antimycotic therapy. This is also helpful in patients with atopic dermatitis who are clearly sensitized against *Malassezia* species (30).

Systemic therapy of atopic dermatitis

Oral H1-antihistamines are frequently used in atopic dermatitis. There are no controlled studies that clearly confirm their effectiveness in this setting. Most studies show only limited decrease in pruritus with antihistamine therapy, reflecting the experience in daily practice (31, e1). The use of strongly sedating H1-antihistamines (doxylamine, diphenhydramine, dimenhydrinate, promethazine) is not recommended in children. The best treatment for pruritus is effective anti-inflammatory therapy (31).

Systemic anti-inflammatory therapy is appropriate for severely affected atopic dermatitis patients (32–34); about 10% of adult patients receive systemic anti-inflammatory therapy at some point during the course of their disease, while in children it is rarely employed.

Short courses of oral glucocorticosteroids (three days to three weeks) can be used to interrupt acute flares in patients with severe atopic dermatitis. Because of the many long-term side effects, longer courses of systemic glucocorticosteroids are not recommended for atopic dermatitis (20, 21).

Cyclosporine is the only systemic immunosuppressive agent approved for the treatment of atopic dermatitis in adults. A variety of contraindications such as hypertension and renal insufficiency restrict its use. Courses of several months of low-dose cyclosporine followed by treatment pauses disease status are preferable to long-term continuous therapy (32). Azathioprine has also been used in Anglo-American countries for adults with atopic dermatitis for many years; controlled studies show a 50% improvement in clinical scores (e23). In addition, methotrexate and mycophenolate mofetil can be used in adults with atopic dermatitis in whom cyclosporine is ineffective or contraindicated (e24, e25). All of these immunosuppressive agents can also be used in children with very severe atopic dermatitis in off-label fashion after a careful consideration of individual contraindications (33, 34).

BOX 4

Delayed reactions (dermatitis reactions) with food allergy and atopic dermatitis

- Caution: Sensitization is not equivalent to clinical relevance
- Only a small percentage of patients with atopic dermatitis react to foods with worsening dermatitis
- No evidence of efficacy for non-individualized diets in atopic dermatitis
- Children on elimination diets are at risk for nutritional deficiencies

BOX 5

Systemic anti-inflammatory therapy for atopic dermatitis

- Systemic glucocorticosteroids (only short courses)
- Cyclosporine (only approved systemic agent for adults)
- Azathioprine
- Mycophenolate mofetil
- Methotrexate

Systemic anti-inflammatory therapy

- Systemic glucocorticosteroids (only short term)
- Cyclosporine (in adults)
- Azathioprine
- Mycophenolate mofetil
- Methotrexate

Microbial colonization of the skin

In addition to *Staphylococcus aureus*, saprophytes of the *Malassezia* species are found in increased amounts in patients with the head-neck-shoulder dermatitis, a variant of atopic dermatitis.

BOX 6

Interventions for atopic dermatitis*¹: Level of evidence (LE) *² and grade of recommendation (GR)*³ for the interventions discussed according to the European guidelines for atopic dermatitis (21, 22)

● **Avoiding trigger factors**

- Use of measures to reduce the amount of house dust mite (LE 2b, GR B)
- Reduction of pollen exposure in sensitized persons (LE -, GR D)
- Avoidance of relevant contact allergens identified by positive patch tests (LE -, GR D)
- Food allergen elimination if proven to be clinically relevant (immediate reaction or worsening of dermatitis) (LE 2b, GR B)

● **Treatment**

- Regular use of emollients/moisturizers (LE 2a, GR B)
- Use of topical glucocorticosteroids (CS) and/or topical calcineurin inhibitors (TCI) (LE 1b, GR A)
- Reduction of recurrences through „proactive therapy“ with CS or TCI (LE 1b, GR A)
- Preferred use of TCI on problem areas (face, intertriginous areas) (LE 1b, GR A)
- No use of H1-antihistamines (LE 1b, GR A)
- No use of antibiotics unless there is superinfection (LE 1b, GR A)
- Use of systemic antibiotics for bacterial superinfections (LE 2b, GR B)
- Use of topical antiseptics when superinfection is suspected (LE 4, GR C)
- Anti-mycotic therapy for “head and neck” dermatitis (LE 2b, GR B) [in text always called head-neck-shoulder dermatitis]
- Use of antiseptic clothing (LE 2b, GR B)
- No use of topical antibiotics (LE -, GR D)
- Systemic antiviral therapy (such as aciclovir) for eczema herpeticum (LE 4, GR D)
- Phototherapy: narrow-band UVB (311 nm) preferred to broad-band UVB (LE 1a, GR A)
- Medium UVA-1 (50J/cm²) equally effective as UVB 311 nm (LE 1b, GR A)
- Systemic CS only for short periods, primarily in adults; poor risk-benefit ration when used for longer periods (LE-, GR D)
- Use of systemic cyclosporine for severely affected adults (LE 1a, GR A)
- In exceptional cases , use of systemic cyclosporine for severely affected children and adolescents (LE 2b, GR B)
- Use of azathioprine in severely affected patients (LE 1b, GR A)
- Use of mycophenolate mofetil in severely affected patients (LE 4, GR C)
- Use of methotrexate in severely affected patients (LE 4*⁴, GR C*⁴)
- Possible use of specific immunotherapy (SIT) in selected sensitized patients (LE 2a, GR B)
- Use of SIT for respiratory allergies with accompanying atopic dermatitis (LE 2b, GR B)
- Adjuvant use of psychotherapy, especially behavioral therapy (LE 3b, GR B)
- Psychological intervention is essential and helpful part of structured atopic dermatitis educational programs (LE 1a, GR A)
- Use of age-adapted interdisciplinary structures atopic dermatitis educational programs for small groups (LE 1a, GR A)

*¹ Not all of the therapeutic measures discussed in the text are evaluated in the European guidelines. In addition, some measures discussed in the European guidelines are omitted here because of space requirements.

*² Level of evidence (LE) as defined in [21]: [just curious why [21] instead of [21] ?] 1a, evidence from meta-analysis of randomized controlled trials (RCT); 1b, evidence RCT; 2a, systematic review of cohort studies; 2b, single cohort studies or RCT of limited quality; 3a, systematic review of case control studies; 3b, single case control study; 4, case series, case cohort studies or cohort studies of limited quality

*³ Grade of recommendation (GR) as defined in [21]: A; 1a, 1b; B; 2a, 2b, 3a, 3b; C; 4; D; expert opinion.

*⁴ Recent controlled studies provide better evidence for the efficacy of methotrexate in atopic dermatitis (e26, e26).

Specific immunotherapy is well established for treating respiratory allergic diseases (allergic rhinitis, mild allergic asthma) when a clinically relevant IgE-mediated sensitization to an allergen has been proven. Controlled studies show that there is no reason not to administer specific immunotherapy for respiratory allergic diseases (allergic rhinitis, mild allergic asthma) in patients who also have atopic dermatitis. A large multi-center study showed a modest improvement in skin disease in severely affected adults treated with specific immunotherapy for house dust mite allergy (35). A recent meta-analysis indicates a highly variable response of atopic dermatitis to specific immunotherapy, so that—especially for children—additional studies are needed before the treatment can be recommended for this specific indication (36).

In addition, biologicals (antibodies that down-regulate atopic inflammation such as those directed against IL-4R, IL-13, IL-31 or thymic stromal lymphopoietin [TSLP]) are being tested for efficacy in atopic dermatitis (e24). They will not be available for routine use in the near future. Phototherapy (UV therapy)—especially UVB 311 nm and UVA1 in medium doses (up to 50 J/cm²)—can be combined with topical corticosteroid therapy, depending on the chronicity and severity of the disease (37). The combination of phototherapy with topical calcineurin inhibitors or with systemic immunosuppressive agents is not recommended. Children under 12 years of age should only be treated with phototherapy in exceptional cases (20).

Structured educational programs and psychotherapeutic measures

Ambulatory structured educational programs have been tested in Germany under the sponsorship of the Federal Ministry of Health (BMS; Bundesministerium für Gesundheit) and the National Association of Health Insurance Funds (GKV-Spitzenverband) (38). On the basis of the positive results of the study showing improved skin status—even one year after participation—the National Association of Health Insurance Funds has recommended since 2007 that such training is to be paid for by health insurance plans. Such programs must include physicians, psychologists/psychotherapists and dieticians (40). Structured interdisciplinary programs are available both for parents and patients; they can be found under www.neurodermitis-schulung.de.

Specific immunotherapy

It is appropriate to perform specific immunotherapy for documented sensitivity to inhalational allergens even when accompanied by atopic dermatitis.

FIGURE 3

Graded therapy of atopic dermatitis. The figure is based on the German AWMF guideline for atopic dermatitis, but has been simplified for readability and does not contain all the original details.

*First-line therapy is usually topical glucocorticosteroids; if not tolerated, or ineffective, or in special locations (face, intertriginous regions) then topical calcineurin inhibitors.

Biologicals

A variety of biologicals are being evaluated in the treatment of atopic dermatitis. None is like to be approved in near future.

Individual psychotherapy is also sometimes indicated for atopic dermatitis; usually behavioral therapy is recommended (22). The use of psychotherapy is generally only recommended when there are clear indications such as psychological issues as individually relevant trigger factors or atopic dermatitis or secondary psychosocial issues for the patient or family are attributable to atopic dermatitis.

An evaluation of the efficacy of management approaches to atopic dermatitis is shown in *Box 6*; it is based on the European guidelines for atopic dermatitis (21, 22).

Conflict of interest statement

Prof. Werfel has received consultancy fees from Novartis, Astellas, Meda and Almirall. He has received lecture fees from Astellas and Novartis. He has participated in clinical studies sponsored by Novartis, Astellas, Regeneron, GSK, Leti Pharma, and ALK Abelló. Astellas has provided paid material costs for a research project he initiated.

Prof. Kapp owns stock in Novartis. He has received consultancy fees from ALK Abelló. He has received reimbursement of travel and registration costs from ALK Abelló. He has received lecture fees from ALK Abelló. He has participated in clinical studies sponsored by Novartis, Astellas, GSK, and ALK Abelló.

Dr. Schwert and Prof. Hansen declare that no conflict of interest exists.

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Psychotherapy

The use of psychotherapy is only recommended when there are clear indications such as psychological trigger factors or psycho-social problems secondary to the atopic dermatitis.

Structured educational programs

Since studies have shown an improvement in skin condition following structured educational programs, the National Association of Health Insurance Funds (GKV-Spitzenverband) has recommended since 2007 that such training be paid for by health insurance plans

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Question 1

Which disorder is associated with atopic dermatitis?

- a) Ulcerative colitis
- b) Asthma
- c) Chronic sinusitis
- d) Viral infections
- e) Irritable bowel syndrome

Question 2

How high is the prevalence of atopic dermatitis before school age?

- a) 1–5%
- b) 5–10%
- c) 10–15%
- d) 20–25%
- e) 30–35%

Question 3

Which factor is most responsible for suffering among atopic dermatitis patients?

- a) Loss of sleep
- b) Muscle tension
- c) Joint pains
- d) Morning stiffness
- e) Pruritus

Question 4

Which of these diagnostic steps is not generally needed in evaluating a patient with suspected atopic dermatitis?

- a) Inquire about family history of atopic diseases
- b) Complete physical examination
- c) Identification of allergen-specific IgG antibodies
- d) Identification of allergen-specific IgE antibodies
- e) Patch testing

Question 5

Which microflora is frequently increased on the skin of patients with head-neck-shoulder dermatitis?

- a) Streptococcus mutans
- b) Capnocytophaga spp.
- c) Lactobacilli
- d) Malassezia species saprophytes
- e) Fusobacterium spp.

Question 6

Sensitivity to which of these contact allergens is equally frequently in patients with atopic dermatitis and controls?

- a) Fragrances
- b) Wool wax alcohols
- c) Nickel ions
- d) Cetyl stearyl alcohol
- e) Methylisothiazolinone

Question 7

For which of these therapeutic inventions is the level of evidence 1a and the grade of recommendation A, according to the European guidelines?

- a) Antiviral systemic therapy for eczema herpeticum
- b) Topical antiseptics when a superinfection is suspected
- c) Use of structured educational programs in small groups
- d) Adjuvant psychotherapy, especially behavioral therapy
- e) Wearing antiseptic garments

Question 8

Which of these agents is approved for immuno-suppressive therapy in adults with atopic dermatitis?

- a) Mycophenolate mofetil
- b) Leflunomide
- c) Azathioprine
- d) Methotrexate
- e) Cyclosporine

Question 9

Which of these approaches is recommended for stage 1 disease (dry skin) in the graded approach to therapy, based on the German AWMF guidelines for atopic dermatitis?

- a) Avoidance or reduction of trigger factors
- b) UV therapy
- c) Topical calcineurin inhibitors
- d) Immunomodulatory therapy
- e) Antiseptic agents

Question 10

Which of these allergens often causes sensitization in patients with atopic dermatitis?

- a) Isocyanate
- b) Penicillin
- c) House dust mites
- d) Thiomersal
- e) Formaldehyde

CONTINUING MEDICAL EDUCATION

The Diagnosis and Graded Therapy of Atopic Dermatitis

Thomas Werfel, Nicolaus Schwerk, Gesine Hansen, Alexander Kapp

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