

REVIEW

Evaluation of the adult patient with atopic dermatitis

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Summary

Atopic dermatitis (AD) is a chronic inflammatory skin disease with a large impact on quality of life of the patients and their families. In most cases, the diagnosis of AD can easily be made based on (family) history and clinical examination. If necessary, a practical set of diagnostic criteria such as the UK diagnostic criteria can be used. During the diagnostic phase, it is important to pay attention to atopic comorbidity, such as allergic airway disease (allergic asthma and/or rhinitis), allergic eye disease (atopic (kerato) conjunctivitis) and immediate-type food allergy. This will not have direct consequences for the treatment of AD, but may be important for the overall well-being of the patient. Psychological factors, such as family circumstances, work/school performance and lifestyle factors should also be explored. Severity scoring using properly validated scoring lists may not be necessary for the diagnosis, however, is recommended for monitoring therapy. Simple scoring systems, such as TIS and IGA are easy to perform in daily practice. Several flare factors in AD, such as exposure to irritants or UV light, can be identified by history and clinical examination: in individual cases, additional diagnostic tests may sometimes be useful to confirm clinical suspicion. There is only limited evidence that allergen exposure to aeroallergens and/or food allergens influences AD severity. Therefore, routine allergen testing is not necessary for diagnosis and treatment of AD. The decision to perform allergen tests mainly depends on atopic comorbidity.

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin affecting about 10–20% of the children in developed countries. AD usually starts during early infancy: 85% begins before the age of 5 years [1]. A large percentage of the children with AD (about 70%) have a spontaneous remission before adolescence, but AD may also start in adults. AD affects between 2% and 15% of adults in industrialized countries [2, 3]. The chronicity and visibility of the disease, together with symptoms such as severe itching, skin damage, soreness and sleep loss may have a profound effect on the quality of life of the patients and their families [4].

Although the majority of AD patients have high serum IgE levels with sensitization to environmental allergens, there is also a subgroup of patients without IgE-mediated sensitization. Different percentages of this so-called intrinsic type of AD have been reported, ranging from 6% to 45% [5–7].

Atopic dermatitis is frequently associated with other atopic diseases, such as asthma, allergic rhinitis (AR), food allergy and atopy-associated eye disorders (allergic

conjunctivitis and atopic keratoconjunctivitis) [8–11]. In AD patients with oesophageal dysfunction (symptoms like dysphagia and food impaction, with or without regurgitation), eosinophilic oesophagitis (EoE) should be considered [12].

The majority of adult AD patients has only mild disease and is treated by general practitioners, whereas more severe and therapy-resistant patients are frequently referred to dermatologists or allergologists. There is no clear consensus on the diagnostic work-up that should be performed when evaluating adult patients with AD. Therefore, large variations exist in the diagnostic approach [13]. According to the PRAC-TALL Consensus Report of 2006 of the European Academy of Allergy and Clinical Immunology (EAACI) and American Academy of Allergy, Asthma and Immunology (AAAAI) [14], diagnostic work-up in children and adults with AD should include history, allergen-specific skin and blood tests and challenge tests depending on the degree of the disease severity and suspected trigger factors involved. To translate these recommendations into daily practice, it is important to specify the intention of the diagnostic work-up in a patient with AD. A

diagnostic work-up may be directed at adequate treatment of AD and/or aimed to diagnose comorbidity, such as allergic rhinoconjunctivitis, allergic asthma (AA) and/or food allergy.

In this review, several aspects of the diagnostic work-up in adult patients with AD, such as diagnostic criteria, clinical scoring, evaluation of comorbidity and relevance of allergen-specific blood tests and challenge tests are discussed.

Diagnosis

There are no biomarkers available for the diagnosis AD. The diagnosis primarily depends on the clinical manifestations of the disease and the family history of the patient concerning atopic diseases. The main symptom of AD is intense itch. The most severely involved body sites include flexural sites of extremities, face, eyelids and neck; although in severe cases, the eczema may be generalized. Although AD usually starts before the age of 5 years, adult-onset AD is not rare, especially in the third decade of life [15]. In adult-onset AD, the diagnosis is sometimes difficult because the typical history of early onset of the disease is missing. Erythroderma may be an important clinical manifestation in adult-onset AD in rare cases [16].

Several sets of diagnostic criteria have been developed in an attempt to better define the disease [17–20]. Diagnostic criteria are based on an objective evaluation of skin lesions by a clinician and a subjective evaluation of the symptoms by the patient. The diagnostic criteria presented by Hanifin and Rajka in 1980 are still the most commonly used diagnostic criteria for AD. These criteria were mainly based on expert consensus; only two validation studies, both hospital based, were published. A refinement of criteria of Hanifin and Rajka was introduced in 1997 by Williams et al. [18]. These so-called UK diagnostic criteria for AD consist of one mandatory and five major criteria, and are more manageable for daily practice. Validation in both hospital and community settings has been performed and the criteria were also tested for repeatability. Recently, Brenninkmeijer et al. summarized the evidence concerning the validity of diagnostic criteria for AD in a systemic review [21]. The authors concluded that the UK diagnostic criteria are the most extensively validated and therefore, this set of criteria for AD should be recommended in intervention studies.

Differential diagnosis

The differential diagnosis of AD is very broad and includes other chronic inflammatory skin diseases, infections, malignancies, metabolic and genetic disorders and autoimmune disorders (Table 1). Other

Table 1. Differential diagnosis in adult atopic dermatitis

<i>Chronic dermatoses</i>
Other forms of eczema
Seborrheic eczema
Contact dermatitis (allergic/irritant)
Nummular dermatitis
Astheatotic eczema
Lichen simplex chronicus
Psoriasis
Pityriasis rubra pilaris
Pityriasis rosea
<i>Infections</i>
Scabies
Dermatomycosis
Impetigo
<i>Malignancies</i>
Cutaneous T cell lymphoma
Mycosis fungoides
Sezary syndrome
Superficial spreading basal cell carcinoma
Immunological disorders
Graft versus host disease
Dermatitis herpetiformis
Bullous diseases
Bullous pemphigoid
Pemphigus foliaceus
<i>Metabolic and genetic disorders</i>
Familial keratosis pilaris
Zinc deficiency (acrodermatitis enteropathica)
<i>Other</i>
Drug eruption
Photodermatitis
Photoallergic contact dermatitis
Chronic actinic dermatitis

eczematous diseases, such as contact dermatitis (allergic and irritant) and seborrhoeic dermatitis may mimic AD: history is often helpful to discriminate. Additional patch testing may be relevant in selected cases. Sometimes, it is difficult to discriminate AD from psoriasis. In addition to history, the presence of sharply demarcated plaques with silver scales and other manifestations of psoriasis such as nail disorders may be helpful to differentiate from AD. Furthermore, histopathology of a skin biopsy may support the diagnosis of psoriasis. Infectious diseases such as scabies and dermatomycosis may also mimic AD. Scabies might be difficult to differentiate if it presents with an eczematous reaction. In scabies, lesions have a more acute onset and, in contrast to AD, are localized in the axillae, groins and genital area with sparing of the face. Often, more family members are affected simultaneously. The diagnosis is based on the presence of mites/eggs in skin scrapings. In contrast to AD, dermatomycosis often presents unilaterally and the pruritis is less intense than in AD. Additional testing, such as KOH examination is helpful to confirm the diagnosis. Cutaneous T cell lymphoma

(CTCL) may resemble AD in adult patients. An increased risk of lymphoma has been described in AD [22, 23]. In a large case-control study, Arellano et al. found that AD was associated with an increased risk of lymphoma (OR, 1.83.) Severe AD further increased the risk of lymphoma (OR, 3.72) [24]. Immunophenotyping of the cellular skin infiltrate should be encouraged, particularly if skin lesions become atypical and erythrodermic flares become recurrent, and in case of unresponsiveness to treatment.

Clinical examination: severity scoring in atopic dermatitis

There is no clear consensus on the classification of the severity of AD. In the ETFAD/EADV task force position paper, the severity of AD was based on (semi) objective criteria (SCORAD value) in combination with subjective criteria (course of eczema). Mild eczema was defined as SCORAD < 15 and being transient. Moderate eczema was defined as SCORAD 15–40 and being recurrent; severe eczema as SCORAD > 40 and being persistent [13].

Properly validated scoring lists are a good tool for monitoring disease severity. In a systematic review, Schmitt et al. assessed the validity, reliability, sensitivity to change and practical use of outcome measures for disease activity in AD [25]. The authors concluded that of the 20 outcome measures that were studied, only Eczema Area and Severity Index (EASI), Patient-oriented Eczema Measure (POEM) and Severity Scoring of Atopic Dermatitis Index (SCORAD) have been adequately validated to be recommended in clinical trials and everyday practice.

However, both SCORAD and EASI are rather time consuming. A more simple scoring system for eczema severity is the Three Item Severity Score (TIS); this scoring system is based on the evaluation of erythema, oedema/papulation and excoriation on a scale from 0 to 3 and has a good correlation with the SCORAD (Rank Spearman $r(s) = 0.86$). The disadvantage of the TIS score is that it does not take into account the body surface area. Another easy scoring tool is the investigator global assessment (IGA), which is a static evaluation (no reference to baseline) of the overall severity of AD at a given time. Although not a real scoring system, the IGA has a good correlation with the EASI [26].

Self-assessment is another tool to monitor disease activity. Therefore, the ETFAD developed a self-assessment scale, using basically the same criteria as SCORAD, in an illustrated document adapted for patients (patient-oriented SCORAD or PO-SCORAD) [27]. In a prospective multi-centre observational study in 471 AD patients, PO-SCORAD and SCORAD were significantly correlated at two evaluation points ($r = 0.67$; $r = 0.71$).

Development of scoring lists for clinical record keeping is one of the main issues of the Harmonising Outcome Measures for Eczema (HOME) working group [28].

Identification of flare factors

Due to the unpredictable course of the disease, aggravating factors, also called flare factors, are difficult to assess. First of all, there is no definition of a flare. Langan et al. [29] proposed to define a flare of AD as 'an episode requiring escalation of treatment or seeking additional medical advice'.

Irritants

Irritant factors, such as rough or woolly clothing, may lead to mechanical irritation and worsening of eczema [14]. Also chemical irritants like skin-cleansing agents can exacerbate eczema, especially on the face and hands. Specific challenge test are not available; identification of irritant factors can only be done by elimination.

In their systemic review on different flare factors in eczema, Langan et al. could not find evidence to support a role for detergents, textiles and irritants in causing worsening of eczema [30]. However, the authors do not exclude irritants as a cause of eczema flares; they state that so far irritants have not been sufficiently studied by means of appropriate study designs.

Inhalant allergens

In daily practice, the relationship between allergen exposure and AD flares is difficult to establish in an individual patient; history is not always helpful. When studying the effect of inhalant allergen exposure on eczema in children and adults with AD, Darsow et al. found that 10–39% of patients reported worsening of eczema after natural exposure to allergens [mostly house dust mite (HDM)] [31].

The strongest evidence supporting a role of inhalant allergens in aggravating AD symptoms is based on experimental models. Bronchial inhalation of HDM in sensitized patients with AD and asthma may result in eczematous reactions [32, 33]. In addition, epicutaneous application of inhalant allergens on the skin (atopy patch test, APT) may elicit eczematous reactions after 48–72 h in about 30–50% of sensitized adult AD patients [31]. On the other hand, reduction of allergen exposure using allergen-avoidance measures shows contradictory results in AD patients [34–37]. There is only limited evidence available that allergen-specific therapeutic interventions, such as allergen immunotherapy, are effective in AD. In a randomized, observer-blinded dose-response study in 89 adult patients with

AD and HDM sensitization, subcutaneous immunotherapy with HDM for 1 year resulted in a significant decrease in SCORAD value in the highest dose group (2.000 and 20.000 SQ-U) [38]. Limitations of this study were absence of a control group and a large dropout: only 51/89 patients completed the study, probably because of the intensive treatment scheme with weekly injections. In a recent open study in 55 AD, Novak et al. reported a significant decrease in SCORAD value during a 15-week course of birch pollen immunotherapy using a depigmented polymerized birch pollen extract. All patients were sensitized to birch pollen and reported AD symptoms related to birch pollen exposure [39]. Due to the lack of a control group, there is no hard evidence on the efficacy of allergen immunotherapy in AD.

Food allergens

In contrast to symptoms of immediate-type food allergy, history is often unreliable in diagnosing eczematous reactions after food allergen exposure because of the unpredictable and remitting course of AD. In studies with limited numbers of selected adult patients with AD, it was shown that severe eczema might be worsened by foods [40]. This may be particularly true for pollen-associated foods. Reekers et al. [41] investigated 37 adult birch pollen-sensitized patients with AD, without immediate-type symptoms after food challenges with birch pollen-related foods. Neither of the patients had a history of food-responsive AD. After elimination period of 4 weeks in which all birch pollen-related foods were excluded from their diet, a double-blind placebo-controlled challenge with a mix of pollen-related foods was performed. Seventeen patients reacted with worsening of eczema and experienced additional itching and sleeplessness within 48 h after oral provocation, with a median increase of 21 SCORAD points. Until now, these results were not confirmed by other studies.

Allergen-restrictive diets are frequently used by AD patients to improve their eczema. In a recent systemic review of randomized controlled trials to assess the effect of dietary exclusion for improving established AD, Bath-Hextall et al. concluded that there is no evidence of benefit in the use of an elemental or few-foods diet in unselected cases of AD. There also appears to be no benefit of egg- and milk-free diet in unselected adult patients with AD. However, overall interpretation of the studies was difficult because of poor methodological quality and most studies were performed in children [42, 43].

UV light

Although the majority of patients with AD benefit from sunlight or therapeutic exposure of ultraviolet radiation,

according to the literature, approximately 10% of the patients with AD experience an adverse reaction upon exposure to sunlight or artificial ultraviolet radiation. In AD patients with exacerbation during spring and summer months for which no other factors may be responsible, photosensitivity should be considered. However, evaluating aggravation of eczema due to (sun) light exposure by history is not always easy, as AD usually affects light-exposed skin sites such as hands, face and neck. In addition, exacerbations of AD during summertime may be provoked by a variety of other factors, including heat-induced sweating and sunburn [44]. All these factors may lead to an overestimation of the prevalence of photosensitive AD. In a more recent study in a large population of 3804 patients with AD, adverse reactions upon exposure to sunlight or ultraviolet radiation were reported in 145 patients (3.8%); phototesting was positive in 108 patients (2.8%) [45]. On the other hand, the diagnosis of photosensitivity in AD can be easily missed, especially in patients who are sensitized to UVA only (17% of 108 patients in above-mentioned study) [45]. In such cases, induction of skin lesions may occur even on cloudy days [44, 45].

If AD symptoms during spring and summer months are persistent despite adequate sun protection and topical treatment, phototesting should be considered. Phototesting may also prevent unnecessary sun avoidance.

Microorganisms

Staphylococcus aureus. In AD patients, *Staphylococcus aureus* can be cultured from 90% of lesional skin and can also colonize non-lesional skin [46]. The density of *S. aureus* appeared to be higher in lesional skin than in non-lesional skin and was positively correlated with lesion severity [47]. By contrast, *S. aureus* can be isolated from the skin of only 5–30% of healthy individuals, mainly from intertriginous areas [48, 49].

Even if there are no clinical signs of infection, *S. aureus* may play a role in promoting skin inflammation in AD by secreting toxins with superantigenic properties resulting in marked activation of T cells and other immune cells [50].

In a recent study by Reginald et al., specific anti-*S. aureus* IgE was detected in more than a third of AD patients, but not in patients suffering from asthma or rhino-conjunctivitis. Patients with more severe forms of AD (higher SCORAD values) showed more frequently IgE reactivity to *S. aureus* than patients with mild disease [51].

Despite the contribution of *S. aureus* to skin inflammation, the authors of a Cochrane database systemic review did not find clear evidence of benefit for antimicrobial interventions in patients with AD [52, 53]. This

can probably be explained by the fact that basic skin care using moisturizers and anti-inflammatory medication alone can reduce microbial colonization and decrease the need for specific antimicrobial therapy [50]. The addition of topical tetracycline to triamcinolone acetonide is effective in reducing skin colonization by *S. aureus* in patients with moderate to severe AD, but did not result in a better disease outcome compared to treatment with triamcinolone acetonide alone [54]. This study demonstrates that treatment of the skin inflammation remains most important in patients with AD. Therefore, it is not necessary to obtain cultures in all patients with AD on a routine basis because there are no therapeutic consequences. Only in AD patients, in whom the eczema is frequently complicated by secondary infections, obtaining culture to determine the sensitivity profile for antibiotics can help to identify resistant organism and direct antimicrobial therapy, if needed.

Herpes simplex virus. The clinical course in AD patients can be complicated by cutaneous viral infections, most often caused by Herpes simplex virus (HSV), human papilloma virus or molluscum virus [55]. Uncomplicated HSV infections are easy to recognize, and in most cases no additional diagnostic tests are necessary. However, in some cases, HSV infections can be missed. For instance in patients with severe eczema and disseminated herpes infection with widespread excoriations and in cases of super infection with *S. aureus* (Fig. 1). In those cases, Giemsa-stained Tzanck smear of cells scraped from the base of a freshly unroofed vesicle or HSV immunofluorescence staining are helpful to identify HSV. Culture or PCR for HSV can also be performed; however, these tests have a time delay and are more expensive. Identification of HSV is also important to diagnose eczema herpeticum, a potentially life-threatening disseminated HSV infection in AD patients [56].

Malassezia. Antibodies against *M. sympodialis* (*Malassezia*) are frequently found in AD patients [57]. Clinically, *Malassezia* sensitization may be suspected in patients with eczema localizations on forehead, eyelids and neck (head and neck dermatitis). These patients may be refractory to conventional treatment such as topical steroids [58]. In contrast to *S. aureus*, there is no convincing evidence that the skin of patients with AD is more heavily colonized when compared with healthy subjects. In the interaction between *Malassezia* and the skin of AD patients, both humoral- and cell-mediated immunity are likely to play a role [59]. AD patients with head and neck dermatitis are more frequently sensitized to *Malassezia* compared with patients without head and neck dermatitis [59]. In a study of 589 AD patients, Devos et al. found that 100% of the patients with head and neck dermatitis had increased

Malassezia-specific IgE compared with only 13% of patients with AD without head and neck dermatitis [60]. Given the multi-factorial cause of AD, it is unlikely that immunity against *Malassezia* would be a single causative factor of head and neck dermatitis in AD, but could be a triggering and perpetuating factor. There is some evidence that systemic antifungal drugs are effective in the treatment of head and neck dermatitis in AD [59, 61, 62]. In a double-blind placebo-controlled study in 80 AD patients with head and neck dermatitis, 200 mg oral ketoconazole resulted in significant reduction in eczema activity and extent [63]. Topical treatment with emollients or 1% hydrocortisone was continued during the study. Treatment of AD patients with head neck dermatitis using oral itraconazole 200 mg once daily for 1 week resulted in a significant improvement of SCORAD value of the head/neck region compared with placebo. No effect was observed on the overall AD severity. In this study, topical steroids were not permitted [64]. The positive effects of antifungal drugs might also be due to other effects than the anti-yeast activity of these drugs.

In the diagnostic work-up of AD patients with head and neck localization, it is not necessary to measure serum IgE antibodies against *Malassezia*; the decision whether or not to treat with systemic antifungal drugs is dependent on the clinical picture and the response to topical corticosteroids, but not on the presence or level of serum-specific IgE.

Comorbidity: other atopic diseases

Asthma and rhinitis

Patients with AD are more likely to have AR and AA; in addition, patients having both AD and AR have a much higher risk for AA (OR 9.04) [65]. AD patients who are sensitized to inhalant allergens are at higher risk to develop AR and AA than those without IgE sensitization [66–69]. Although AD and atopic airway disease often coincide, clinical activity of both diseases may vary over time. Furthermore, airway symptoms and AD activity may both parallel and alternate in the same patient. In an experimental setting, bronchial challenge with aero-allergens (HDM) can worsen AD symptoms in patients with AD and concomitant AA [32, 33].

As allergic airways disease is often underdiagnosed and AD patients are more at risk to develop these diseases, an exploration of respiratory comorbidity should be performed in every AD patient. This implies a careful history of wheezing during the night and/or during exercise, coughing, nasal obstruction and/or nasal discharge. For more detailed and standardized information on respiratory allergy, the ISAAC questionnaires can be used (<http://www.isaac.auckland.ac.nz/resources/tools>).



Fig. 1. Eczema herpeticum with super infection by *Staphylococcus aureus*.

php). Early detection and adequate treatment of allergic airway diseases can reduce comorbidity in AD patients.

Allergic conjunctivitis and atopic keratoconjunctivitis

The reported incidence of ocular involvement in AD is 25–42% [70, 71]. In the evaluation of a patient with AD, the history concerning eye symptoms may be helpful to identify atopic eye diseases and if necessary referral to an ophthalmologist.

Allergic conjunctivitis (AC) is the most common eye disease in patients with AD. Symptoms of AC are usually bilateral and include itching, burning, erythema and watery or sometimes mucoid discharge, often occurring within 30 min after exposure to inhalant allergens. In general, there is no corneal involvement. AC is often associated with AR and can be regarded as a part of the atopic syndrome and not as a direct consequence of AD.

In adult patients with AD, eyelid dermatitis is very common. The skin of the eyelids is often red and swollen, macerated with crusting and scaling. In severe cases, the inflammation may spread to the eyelid margins and eyelashes; an atopic blepharo-conjunctivitis may develop resulting in a thickened and inflamed lid margin with cicatrization [72] (Fig. 2a). Although the exact mechanism is still unknown, AD patients with severe eyelid dermatitis seem to be more at risk for developing atopic keratoconjunctivitis (AKC). AKC is characterized by lesions of conjunctiva and cornea, which vary in severity. Ocular symptoms include

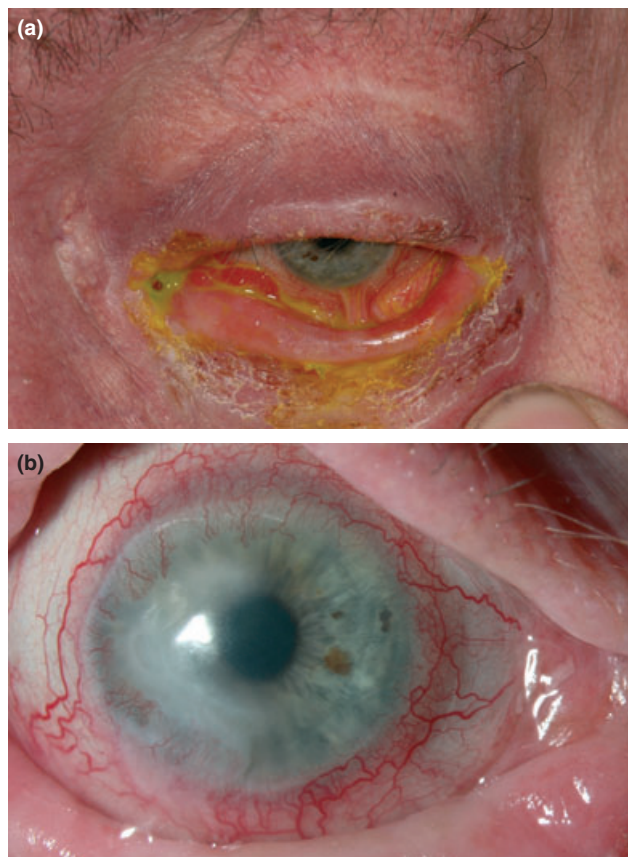


Fig. 2. (a) Chronic eczema of eyelids with oedema, crusting, scaling and cicatrization. (b) Neovascularization of the cornea: characteristic of atopic keratoconjunctivitis.

intense itching, photophobia, burning, foreign-body sensation and blurring of vision. There is usually copious mucous discharge gluing the eyes together upon awakening. Punctate epithelial keratitis is an early corneal finding in AKC, which may progress into persistent corneal defects and neovascularization (Fig. 2b). These defects are often complicated by herpes simplex or bacterial superinfections.

Early diagnosis and adequate treatment of AKC in AD patients may prevent irreversible damage to the cornea leading to permanent blindness.

Immediate-type food allergy

The prevalence of immediate-type food allergy in infants with AD may be estimated at 30% [73]. Less data are available on the prevalence of concomitant immediate-type food allergy in adult patients with AD. Recently, the interest in the relationship between AD and food allergy has been renewed. The identification of the loss-of-function mutations in the gene encoding filaggrin (FLG) as a possible causal mechanism for the development of AD has triggered this interest. Loss-of-function mutations in the FLG gene may result in increased permeabil-

ity of the skin for proteins, which may be associated with increased risk of transcutaneous sensitization. Cutaneous exposure to food allergens in patients with FLG gene defects may represent an important route for the development of sensitization and food allergy in those patients [74].

Diagnosis of immediate-type food allergy is complicated by the observation that detection of food-specific IgE (sensitization) does not necessarily indicate clinical allergy. Especially, sensitization to pollen-related cross-reactive food allergens (apple, hazelnut, carrot, celery) is frequently seen in adult AD patients [40, 73, 75]. Although immediate-type food allergy does not influence eczema severity, adequate diagnosis and treatment of concomitant food allergy in AD patients may have positive effects on AD by reduction of stress and increasing well-being of the patient. In addition, unnecessary diet restrictions in patients with AD can be avoided by performing careful diagnosis in case of suspected food allergy.

Eosinophilic oesophagitis

Eosinophilic oesophagitis is a rare condition that predominantly affects people with an atopic background; several studies have reported that 50–60% of patients with EoE have a prior history of atopic diseases [76]. Several observations suggest that the underlying pathomechanisms of EoE are similar to those of allergic airway diseases and AD [77]. Elevated total serum IgE levels and sensitization to food and/or aeroallergens have been reported in the majority of patients with EoE [77, 78].

Eosinophilic oesophagitis should be considered in atopic patients with oesophageal dysfunction (symptoms like dysphagia and food impaction, with or without regurgitation) not responsive to a 6-week course of PPI's [79]. For the diagnosis, biopsy specimens must show eosinophil-predominant inflammation: 15 eosinophils per high-power field is considered a minimum threshold for the diagnosis of EoE.

Although the frequency of EoE in AD is not known, doctors who treat AD patients should be aware of this rare, but increasingly recognized associated condition.

Allergen testing

Inhalant allergens

In contrast to allergic airway and eye disease, history is often not very helpful in identifying a role of inhalant allergens in AD symptoms. Although immediate-type symptoms, such as contact urticaria, after skin contact with inhalant allergens may occur, there is little evidence of worsening of eczema after cutaneous allergen

exposure. Patients with AD and concomitant AA may experience worsening of eczema after inhalation of aeroallergens [32, 33].

Both skin prick tests (SPT) and measurement of serum antigen-specific IgE (sIgE) antibodies can be used to determine sensitization to inhalant allergens. Epicutaneous application of inhalant allergens on the skin (atopy patch test, APT) can elicit eczematous reactions after 48–72 h in about 30–50% of sensitized adult AD patients [31]. However, the APT is not proposed as a single screening test in patients with AD, but may be used in addition to SPT and sIgE to suggest clinical relevance of given sensitization. However, until now, there are no studies supporting that patients with positive APT benefit more from allergen avoidance [36].

In the diagnostic work-up of AD patients, inhalant allergen testing is not always necessary, because in most cases there are no consequences for the treatment of the eczema. However, in case of a history of contact urticaria after allergen exposure (especially furry animals) and in case of positive history of immediate-type airway and/or eye symptoms, allergen testing can be helpful.

Contact allergens

Impaired skin barrier function and hyper-reactivity to irritant stimuli can enhance contact allergy in AD patients [13]. In a population-based study in 1236 adults, Dotterud et al. found contact sensitivity was associated with AD only in women (OR 1.58) [80]. At least one positive patch test to standard series was found in approximately 40% of AD patients aged 15 years or more [81, 82]: nickel and constituents of cosmetics are frequently described contact allergens in AD patients [81].

In a retrospective study in Germany, a large group of patients who were referred for the evaluation of suspected contact allergy was evaluated. The pattern of positive patch test results to the most frequent contact allergens in patients with AD ($n = 9020$) were compared to non-atopic patients ($n = 15\,263$) [83]. Overall, the contact allergen profile in AD patients was quite similar to the spectrum found in patients without AD. Only contact sensitization to bufexamac occurred three times more often in AD patients; however, this product is no longer available from 2010.

When the patch tests results were clustered into six main groups, significant higher frequencies of positive patch test results to fragrances, rubbers, emollients and external drugs were found in AD patients compared with the control group.

Because AD patients tend to use topical steroids for a long period of time, they may develop allergic contact dermatitis to corticosteroids. In a recent study, 3547

patients were patch tested with tixocortol-21-pivalate (marker for group A corticosteroids), budesonide (marker for groups B corticosteroids) and hydrocortisone-17-butyrate (marker for group D2 corticosteroids) [84]. In total, 72 individuals (2%) of the study population had a corticosteroid allergy. Significantly more patients with a tixocortol-21-pivalate allergy had AD ($P = 0.02$) and leg dermatitis ($P = 0.01$).

Dependent of the history, patch testing may be considered in AD patients. In cases of worsening of eczema despite adequate treatment, patch testing with topical steroids can be useful.

Food allergens

Accurate diagnosis of immediate-type food allergy requires primarily a careful history. Detection of specific IgE by serological tests and/or skin prick tests can support the findings of clinical history. In case of doubt, oral food challenges, preferably double-blind placebo-controlled, are required to confirm the diagnosis [85]. *In vitro* tests offer the opportunity to test single purified or recombinant allergens, also known as component-resolved diagnostics, which may have a better diagnostic value [86, 87].

As was mentioned earlier, isolated eczematous reactions after food exposure in adult AD patients are very rare. The APT with food allergens may have some positive predictive value for isolated eczematous reactions; however, it is not recommended for routine diagnosis of food-induced eczema by the recent EAACI position paper [88]. Such a relationship can only be properly diagnosed by oral food challenges. The recommended challenge protocol from the EAACI [40] for the diagnosis of food-related eczematous reactions in AD includes a diagnostic elimination diet over a period of 4–6 weeks excluding the suspected food items followed by food challenges, ideally with a placebo-controlled design. The skin must be scored by an established eczema score (e.g. SCORAD) before challenge and at least 24 h thereafter; a difference of at least 10 SCORAD points is usually considered as a positive reaction.

Routine food allergen testing in AD patients without a history of immediate-type symptoms is not necessary. If food allergens are considered as a trigger for AD flares, allergen testing should always be followed by a double-blind placebo-controlled food challenge as described above.

Bone mineral density

Due to the chronic inflammatory nature of the disease and the long-term use of topical steroids on large body surface areas, AD patients are theoretically at risk for developing osteopenia and osteoporosis. Other lifestyle

factors such as limited exercise due to increased itching after sweating or reduced dairy product intake may also contribute to low bone mass in AD patients. In a recent study performed in 125 adult patients with moderate to severe AD, low bone mineral density (BMD) was found in about one-third of the patients [89]. Osteoporosis was found in 4.8% and osteopaenia was found in 32.8% of the patients. The existence of low BMD seemed to be independent of the used treatment, because no significant association between BMD and the cumulative dose of topical and oral steroids during the 5 years prior to inclusion was found. There was also no significant difference in lifestyle factors, such as alcohol, coffee and dairy products intake, smoking, exercise and sunlight exposure between the groups with low BMD compared with normal BMD.

In daily practice, routine measurement of BMD is not necessary in AD patients. As osteopenia is relatively common in adult patients with AD, lifestyle advices should be given to all patients.

Vitamin D

In AD, vitamin D seems to be able to suppress inflammatory responses, promote the integrity of the epithelial barrier and enhance antimicrobial peptide activity [90]. *In vitro* studies show that calcitriol, the active compound of vitamin D, can induce cathelicidin expression in keratinocytes, which enhances antimicrobial activity against *S. aureus* [91, 92]. Defects in the capacity to increase the production of cathelicidins may account for an increased risk of infections in AD patients [93, 94]. Oral administration of vitamin D3 (4,000 IU/day for 21 days) in 14 patients with moderate to severe AD resulted in a significant increase in cathelicidin expression in biopsies from lesional skin [95].

There are some studies showing low vitamin D serum levels in AD patients. Peroni et al. [96] measured 25-hydroxyvitamin D levels in 37 children with AD; insufficient and deficient serum levels were found in, respectively, 40% and 21% of the children. An inverse correlation between serum concentrations of 25-hydroxyvitamin D and severity of disease evaluated by SCORAD was found in this study. Oral administration of vitamin D may result in beneficial effects on AD in limited number of patients [97, 98]. Further research is needed to explore the clinical relevance of low vitamin D levels in AD.

At this moment, routine measurement of 25-hydroxyvitamin D serum levels is not advised in the diagnostic work-up of AD patients. In case of risk factors for low vitamin D levels such as limited sun exposure, for instance in photosensitive AD, measurement of serum concentrations of 25-hydroxyvitamin D may be considered.

Evaluation of quality of life in atopic dermatitis patients

The negative psychosocial effects of AD on quality of life (QoL) are well established [99, 100]. Factors such as severe itching, scratching, sleep loss and social embarrassment may lead to social isolation, problems at school and/or work and financial problems in individual patients. For instance, AD may be responsible for indirect costs such as purchase of special household items and days lost from work [101]. Concerning the degree of handicap in relation to the choice of educations and occupation, 38% of AD patients had abstained from a specific education or job due to AD. Even mild to moderate disease may cause handicap, as seen from increased sick leaves and early retirement pensions [102].

Several years ago, the European Academy of Dermatology and Venerology (EADV) has recommended that dermatologists should incorporate health-related quality-of-life measurements to help assess and monitor the progress of their patients. Nowadays, QoL is a frequently used tool in clinical studies; however, its use in daily practice is limited.

The most frequently used instrument for the measurement of QoL in AD patients is the Dermatology Life Quality Index (DLQI). The DLQI is a health quality-of-life scale specific to dermatological disorders, which involves 10 items focused on six dimensions: symptoms, daily activities, leisure, work, personal relationships and treatment [103]. The DLQI is frequently used

in clinical studies in AD and is also manageable in daily practice. Until now, there are no studies comparing different QoL questionnaires in AD.

Summary and conclusions (Fig. 3)

In most cases, the diagnosis AD can easily be made based on (family) history and clinical examination. A practical set of diagnostic criteria, such as the UK diagnostic criteria, can be used in case of doubt.

For determination of the severity of the eczema, several clinical scoring lists are available. Simple scoring systems, such as TIS and IGA are easy to perform in daily practice during follow-up of treatment.

The unpredictable course of AD with recurrent exacerbations and remissions makes it very difficult to identify the different factors that may exacerbate the disease (flare factors). Some flare factors in AD, such as irritants, UV light and infections can be identified by history and clinical examination: in individual cases, additional diagnostic tests may sometimes be useful to confirm the clinical suspicion. History and clinical examination, however, are not useful in identifying the role of allergen exposure on flares of eczema. There is only limited evidence that exposure to aeroallergens and/or -and food allergens directly affect AD severity and most of this evidence is based on experimental models. Therefore, routine allergen testing is not necessary for diagnosis and adequate treatment of AD. The

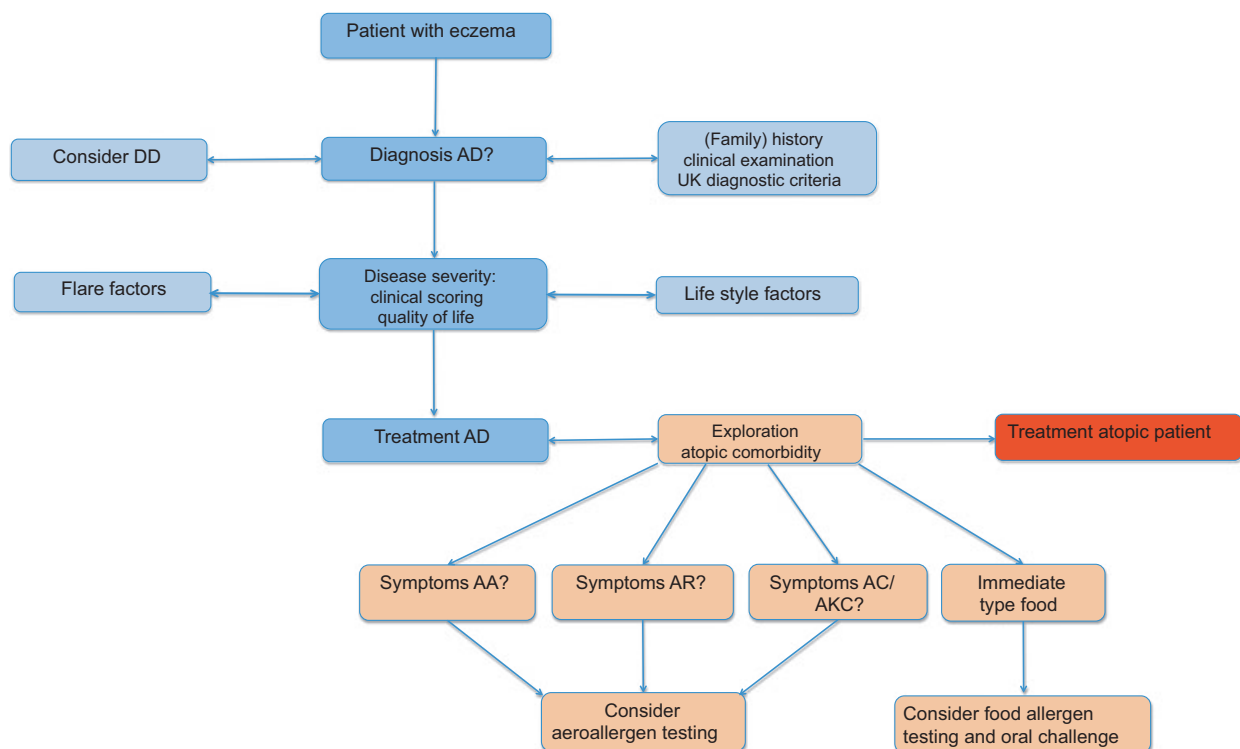


Fig. 3. Summary of suggested diagnostic work-up in adult patients with atopic dermatitis.

decision to perform allergen tests mainly depends on the atopic comorbidity (Fig. 3).

Exploration of atopic comorbidity, such as allergic airway disease (AA and/or rhinitis), allergic eye disease (atopic (kerato) conjunctivitis) and immediate-type food allergy may not have direct consequences for the treatment of AD, however, can be very important for the overall well-being of the patient. For instance, early diagnosis and treatment of atopic eye disease may avoid serious complications such as damage to the cornea. In addition, adequate diagnosis and treatment of concomitant food allergy in AD patients may be important on one hand to prevent severe immediate-type reactions, and on the other hand to avoid unnecessary elimination diets. Early diagnosis and treatment of concomitant airway disease may reduce stress in patients and increase well-being.

AD is a chronic disease with a large impact on quality of life of the patients and their families. During the diagnostic phase, it is important to get an overall picture of the patient. Apart from atopic comorbidity, other factors concerning the overall well-being of the patient, such as family circumstances, work/school performance and lifestyle factors should be explored.

The scope of this review is the diagnostic work-up in adult patients with AD. The diagnostic work-up in children with AD was published recently in this journal [104]. Although the items in the diagnostic work-up in adults and children are more or less the same, there are differences in focus and accent. Diagnostic criteria for AD in adults and children are nearly the same (with sometimes minor adjustments for children, for instance the UK diagnostic criteria): the differential diagnosis, however, is different. Regarding the comorbidity, concomitant airway symptoms in children with AD may

be more difficult to recognize than in adults. In contrast, in adult patients with AD, special attention should be paid in AD-related eye diseases such as atopic blepharitis and atopic keratoconjunctivitis, as the eyelids are more often involved in adult AD.

There are also some accent differences in diagnostic allergen tests between adult and childhood AD, especially concerning food allergens. In children, food allergy is more often presumed to be a trigger of AD; diets (often unnecessary) are more often prescribed in children. In addition, the history of type I allergy to food allergens in children is more difficult than in adults. Therefore, double-blind placebo-controlled food challenges are more often indicated in children.

In contrast, contact allergens as a trigger in AD are more frequent in adults compared with children, due to exposure during work.

Microorganisms, such as staph Aureus or Herpes Simplex, can complicate AD in both adults and children. The possible role of *Malassezia* in patients with head and neck dermatitis is more restricted to the adult AD patients.

Evaluation of psychosocial factors is important in both adults and children with AD. While in children the focus is more on school performances and teasing, in adults work-related problems and sexual/relational problems should be explored.

Limitations

This manuscript cannot be regarded as a systematic review; however, data from systematic reviews were included when available.

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