Diagnostic Work-up and Treatment of Severe and/or Refractory Atopic Dermatitis

Arjan Devillers

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The work presented in this thesis was performed at the department of Dermatology, Erasmus MC, Erasmus University Rotterdam, The Netherlands.

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Chapter 1

General introduction

Atopic dermatitis

Atopic dermatitis (AD) or atopic eczema , is a chronic inflammatory skin disease characterized by dry skin, itching and recurrent red and scaly skin lesions. It is a relatively common skin disease with an estimated prevalence of 10-20%.[1] The majority of patients show their first clinical symptoms in infancy or early childhood, with reported percentages of 60% before the age of 1 year and 85% before the age of 5 year.[2]

The pathogenesis of AD is characterized by a complex interaction between a genetic background and different environmental factors.[3,4] Over the last years genome wide linkage mapping as well as selective region specific linkage mapping based on candidate genes, has revealed many possible AD related loci on different chromosomes.[5] Summarizing there seem to be two major groups of genes present within the genetic background of AD: genes encoding for epidermal or other epithelial structural proteins and genes encoding for major elements of the immune system. [4,5]

The term "atopic dermatitis" was coined by Wise and Sulzberger in 1933 and reflects the association between AD and other so-called atopic disorders, such as asthma and allergic rhinitis.[6] The diagnose is based on clinical criteria, with the extensive criteria of Hanifin and Raijka as the classical starting point published in 1980.[7] In the years to follow several modifications were proposed, leading to publications on different new sets of criteria.[8] For our own research purposes we currently use the diagnostic criteria formulated by the UK working party on AD, which have been extensively validated in the past and are widely accepted as a diagnostic tool (figure 1).[8,9]

Must have
• An itchy skin condition (or report of scratching or rubbing in a child
Plus three or more of the following
• History of itchiness in skin creases such as folds of the elbows, behind the knees, fronts of ankles, or around neck (or the cheeks in children under 4 years)
• History of asthma or hay fever (or history of atopic disease in a first degree relative in children under 4 years
• General dry skin in the past year
• Visible flexural eczema (or eczema affecting the cheeks or forehead and outer limbs in children under 4 years)
• Onset in the first two years of life (not always diagnostic in children under 4 years)

Figure 1. The diagnostic criteria for AD as described by the UK working party on AD

The term atopy itself is used to describe the genetic predisposition to become IgE – sensitized to allergens commonly occurring in the environment.[10] This sensitization can be detected by performing skin prick tests (SPT) or measuring serum specific IgE against common aero-or food allergens. Whether or not the presence of this sensitization should be a mandatory criterium for the diagnosis of AD is still debated.[11] This controversy is nicely illustrated by a question phrased by Hywell Williams: "How atopic is atopic dermatitis?".[12] His conclusion was that it would be premature to divide patients with AD based on sensitization alone, which still seems valid today. The role of IgE in the pathogenesis of AD may indeed not be that of a major causative factor but only that of a very common epiphenomenon.[12]

Assessment of disease severity

Disease severity would ideally be assessed using a disease specific and objective laboratory marker. Unfortunately such a laboratory test is currently not available for assessment of disease severity in AD. The commonly used "next best thing" are scoring systems based on the objective and/or subjective clinical features of AD. "Objective" In this context means scored by a physician and "subjective" means scored directly by the patient or caregiver. Of course the so-called "objective" features still include a certain degree of subjectivity, because the physician has to score them based on his personal observations. In a recently performed review on behalf of the European Dermato-Epidemiology Network, the authors were able to identify 20 different scoring systems used to measure disease severity in AD.[13] They concluded that only three out of these 20 had been validated adequately enough to recommend their use in clinical trials and daily clinical practice. One of these three was the Patient-Oriented Eczema Measure (POEM), which is a subjective, questionnaire based system. The other two were the more objective Eczema Area and Severity Index (EASI) and the SCORing AD (SCORAD) index, including its derivative the so-called objective SCORAD.[13] As the objective SCORAD was used in the studies described in this thesis, the SCORAD index and the objective SCORAD will be outlined in more detail in the paragraph below.

In the original publication on behalf of the European Taskforce on Atopic Dermatitis (ETFAD) the SCORAD is described as an index incorporating the extent of the disease according to the rule of nines (A, 20%), together with the intensity of six clinical features on a scale of 0-3 (B, 60%) and the two subjective symptoms itch and sleeplessness on a scale of 0-10 (C, 20%).[14,15] The score is achieved by using the formula A/5 + 7B/2 + C, leading to a maximum score of 103 (figure 2). Although subjective symptoms yield very

important information from a patient's perspective, they are probably not the best choice to monitor disease activity in clinical trails, as they may be biased by the social or cultural background of patients and caregivers.[16] This is why the ETFAD recommends using the objective SCORAD, instead of the original SCORAD index, in determining disease severity in clinical trials.[16] In the objective SCORAD the subjective symptoms are excluded, leading to the formula A/5 + 7B/2, with a maximum score of 83. An additional 10 points may be added in patients with severely disfiguring lesions on the face or hands.[16]

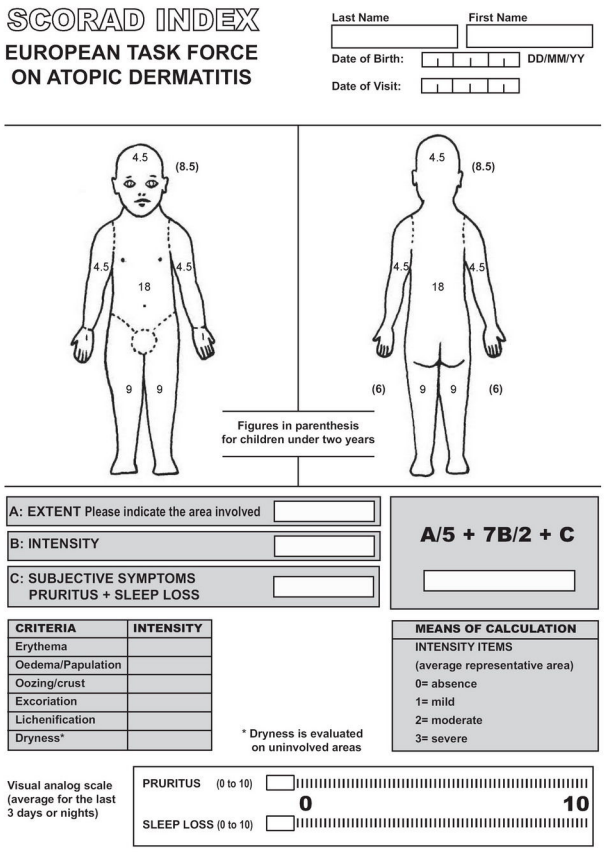

Figure 2. Assessment of disease severity in AD using the SCORAD index (A/5+7B/2+C) or objective SCORAD (A/5+7B/2).

Diagnostic work-up

As discussed previously the diagnosis of AD is based on criteria, which are obtained by a correct medical history and physical examination. Skin biopsies are not routinely used to substantiate the eczematous nature of the skin lesions in AD, although the histology of acute as well as chronic skin lesions is well established. The diagnostic work-up is primarily aimed at identifying environmental factors that may worsen the skin disease in individual patients. Non-specific factors, such as irritative substances and stress, can be identified by

including specific questions in the medical history or by using standardized questionnaires. The more specific factors include different food-, aero- and contact allergens that may cause relevant allergic reactions in patients with AD. Indications for an allergologic work-up include severe and/or refractory skin disease as well as reported flare-ups of skin lesions after contact with suspected allergens. Sensitization against aero- or food allergens is strongly associated with AD and can be readily detected in a large number of patients. However, great care must always be taken to avoid confusion between a detectable sensitization and a clinically relevant allergy.

Food allergens

Clinically relevant food-allergies in AD are almost exclusively limited to a small sub-population of relatively young children. These children may benefit from dietary measurements and need to be separated from the majority of children with AD in whom diets are not beneficial. In the Netherlands the most commonly implicated food allergens include cow's milk, hen's egg and peanut.

The allergologic work-up in children with AD and suspected food allergy starts with a careful history and clinical examination. Traditionally this is combined with the results from Skin Prick Tests (SPT) and/or the measurement of serum specific IgE. Both tests are aimed at detecting immediate type sensitization against the suspected food allergens. The Skin Application Food Test (SAFT) has been described as a reliable and child friendly alternative to the SPT in children with AD below the age of 3 years.[17] The golden standard for the diagnosis of a food allergy is the double blind placebo controlled oral challenge (DBPCOC), followed by a supervised reintroduction period.[18] Although DBPCOC are time-consuming and carry a certain risk, they may be necessary in cases were serology, skin tests and history do not reveal a conclusive result.

In recent years the Atopy Patch Test (APT) has been advocated as an useful addition to the allergologic work-up of children with AD and suspected food allergy. This skin test is aimed at detecting delayed type, eczematous skin reactions, following epicutaneous application of food (or aero-)allergens in patients with AD. The APT was first described in detail in 1982 and has been the focus of increased research interest over the last 10-15 years.[19] Combining the results from the APT with results from traditional tests has been reported to reduce the number of OC necessary in order to reach a conclusive result regarding relevant food allergies.[20,21] Although in theory the combination of a skin test aimed at immediate type allergic reactions (IgE, SPT or SAFT) and a skin test aimed at delayed type allergic reactions (APT) seems promising, there have been conflicting results published regarding the additional value of the APT in daily clinical practice.[20-26]

Aero allergens

Traditional tests used to detect sensitization against aeroallergens include SPT, Intracutaneous Tests (IT) and measurement of serum specific IgE. The relevance of a sensitization with aero allergens in patients with AD remains controversial as there is currently no gold standard available for confirmation of this relevance. However, there does seem to be a subgroup of patients with AD where contact with aeroallergens, such as house dust mite or grass pollen, is capable of worsening eczematous skin lesions.[27] Adequate avoidance measures may be helpful in controlling AD in these patients, although results from clinical trails are contra dictionary.[28-30]

Additional evidence for a possible role of aeroallergens in the pathogenesis of AD is found in the fact that epicutaneous application of these allergens via the APT can elicit eczematous skin reactions in patients with AD.[31] Differences in methodology and the previously mentioned lack of a golden standard for a relevant sensitization are two major obstacles in the development of the APT as an addition to our allergologic work-up in patients with AD.[19,32] Most of the current clinical data on the APT with aeroallergens is based on adult patient populations and pediatric data is scarce.

Contact allergens

Although patients with AD are not more likely to become sensitized against common contact allergens than the general population, this possibility should be kept in mind in patients with severe and/or refractory skin disease.[33] Relevant contact allergies are more frequent in adolescence and adulthood but may also occur in childhood.[34] Patch tests can be used to confirm a sensitization against contact allergens, such as ingredients in over the counter skin care products or topical medication.

Disease management

The treatment of AD is aimed at restoring the epidermal barrier defect and reducing skin inflammation. Emphasis has to be put on the proper use of topical medication as well as avoidance of the different environmental factors that may negatively influence disease severity. Several educational programs have been shown to be an effective addition to the treatment of patients with AD, reducing severity of skin disease and improving quality of life.[35] A short overview of the currently available treatment options is listed below.

First line treatment

In most patients with uncomplicated mild to moderate AD, disease control can be obtained by use of emollients and once daily applications of topical corticosteroids if necessary.[36] Emollients are used to alleviate skin dryness and restore part of the defective epidermal barrier. Whether or not emollients based on the lipid composition of the human stratum corneum have a superior effect compared to more conventional emollients remains to be established.[37] Research in this field seems promising, especially in light of recent advances in our knowledge on epidermal barrier defects in patients with AD.[38]

Topical corticosteroids are available in different potencies, which correlate with their risk for local and systemic side effects.[39] The appropriate potency for an individual patient has to be established based on the age of the patient and the sensitivity to possible corticosteroid side effects of the body area which is to be treated.[39] In a long term maintenance treatment, intermittent use of once daily topical corticosteroids (2-4 days per week) has been shown to reduce the number of eczematous flare-ups.[40]

Topical alternatives

An alternative to topical corticosteroids became recently available after the discovery of topical calcineurine inhibitors.[41] These molecules function as topical immunosuppressants by selectively blocking T-cell activation and proliferation. Currently both pimecrolimus (Elidel®) and tacrolimus (Protopic®) are registered for use in patients with AD above the age of two years. The first is available as an 1% ointment, whereas the latter is available as an 0.03% and 0.1% ointment. Efficacy and safety studies look very promising, although both products are not more effective than potent topical corticosteroids. Their unique safety profile makes them a valid treatment alternative, especially on body areas prone to corticosteroid side effects such as the face and body folds.[41] Possible long term side effects remain to be further clarified in the future.

Topical coal tar (TCT) preparations form another alternative or adjuvans to topical corticosteroids. They originate from the time before the discovery of topical corticosteroids more than fifty years ago. Their exact mode of action is unknown but they have anti-pruritic as well as anti-inflammatory properties, making them effective in the treatment of AD.[42] Although much has been said about the possible carcinogenic nature of TCT, there has been no conclusive evidence of increased malignancies after dermatological use.[42] However, data on increased levels of carcinogenic substances in urine samples of patients treated with TCT, together with their unpleasant odour and the increased risk of sun-burn and folliculitis limits their use in current clinical practice.[43]

Intervention treatment

Patients with severe and/or refractory AD may need a different therapeutic approach. Well known intervention treatments include systemic corticosteroids, cyclosporine A, azathioprine or photo(chemo)therapy.[36] All off these interventions have (relative) contraindications and potential side effects, limiting their use in children. Wet-wrap treatment (WWT) with diluted topical corticosteroids has been advocated as a relatively safe and effective intervention treatment in children with severe and/or refractory AD.[44] However, it is a laborious and time-consuming treatment, which calls for close supervision.[ ] WWT should not be misused and has to be reserved as a short term intervention treatment in carefully selected patients.[45]

Secondary skin infections

Patients with AD are at risk for secondary skin infections, due to their disrupted epidermal barrier, combined with a suppression of their non-specific, innate immune system and a skewing of their specific immunity towards a so-called Th-2 response.[4] The most frequent pathogens are bacteria (e.g. *Staphylococcus aureus*), but viral (e.g. *Herpes Simplex*) as well as yeast and fungal (e.g. *Malazessia* and *Trichophyton* species) infections may also occur. Additional antimicrobial treatment should be started when clinical signs of active skin infection are present. Mild bacterial infections may be treated with topical fucidic acid, which has been shown to be very effective against *Staphylococcus aureus*. More widespread infections should be treated with short courses of systemic antibiotics. Recolonization with *Staphylococcus aureus* will rapidly occur after cessation of topical or systemic antibiotics and maintenance treatment should be avoided as this may lead to skin colonization with resistant strands of bacteria. Widespread secondary *Herpes simplex* infections, also known as eczema herpeticum, can be a serious and possibly even life-threatening complication in AD and should be treated by systemic antiviral agents such as acyclovir and others. Secondary yeast and fungal infections may be treated using topical or systemic antimycotics.

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Chapter 2

Aims of the thesis

Aims of the thesis

This thesis is based on the clinical care for patients with severe and/or refractory AD, focussing mostly on the pediatric population. The diagnostic work-up as well as disease management in these patients differs from that in patients with mild or moderate disease, as has been described above. The following aims of the thesis were formulated.

1. To evaluate the additional value of the atopy patch test within the current diagnostic protocol of the Pediatric Dermatology Unit of the Erasmus MC-Sophia Children's Hospital for the diagnosis of a relevant food allergy in young children with AD. [chapter 3]
2. To evaluate the presence of positive atopy patch test reactions to aero-allergens in young children with atopic dermatitis, including their correlation with elevated levels of serum specific IgE and/or the presence of positive skin prick tests against these allergens.[chapter 3]
3. To evaluate plasma MMP-9 as a possible objective laboratory marker for the severity of AD [chapter 4]
4. To further substantiate and optimize wet-wrap treatment with diluted topical corticosteroids as an intervention treatment in severe and/or refractory AD. [chapter 5]

Chapter 3

The atopy patch test in the diagnostic work-up of pediatric patients with atopic dermatitis

The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study

U. Darsow, J. Laifaoui, K. Kerschenlohr, A. Wollenberg, B. Przybilla, B Wüthrich, S. Borelli Jr, F. Giusti, S.Seidenari, K. Drzimalla, D. Simon, R. Disch, S.Borelli, A. Devillers, A. Oranje, L. de Raeve, J.-P. Hachem, C. Dangoisse, A. Blondeel, M. Song, K. Breuer, A. Wulf, T. Werfel, S. Roul, A. Taieb, S. Bolhaar, C. Bruijnzeel-Koomen, M. Brönnimann, L. Braathen, A. Didierlaurent, C. André, J. Ring

Allergy 2004; 59:1318-1325

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Delayed and immediate type reactions in the atopy patch test with food allergens in young children with atopic dermatitis.

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Atopy patch tests with aeroallergens in children aged 0-3 years with atopic dermatitis

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Background

The atopy patch test (APT) was proposed to evaluate IgE-mediated sensitizations in patients with atopic eczema (AE).

Objective

The prevalence and agreement with clinical history and specific IgE (sIgE) of positive APT reactions was investigated in six European countries using a standardized method.

Methods

A total of 314 patients with AE in remission were tested in 12 study centers on clinically uninvolved, non-abraded back skin with 200 index of reactivity (IR)/g of house dust mite Dermatophagoides pteronyssinus, cat dander, grass, and birch pollen allergen extracts with defined major allergen contents in petrolatum. Extracts of egg white, celery and wheat flour with defined protein content were also patch tested. APT values were evaluated at 24, 48, and 72 h according to the European Task Force on Atopic Dermatitis (ETFAD) guidelines. In addition, skin-prick test (SPT) and sIgE and a detailed history on allergen-induced eczema flares were obtained.

Results

Previous eczema flares, after contact with specific allergens, were reported in 1% (celery) to 34% (D. pteronyssinus) of patients. The frequency of clear-cut positive APT reactions ranged from 39% with D. pteronyssinus to 9% with celery. All ETFAD intensities occured after 48 and 72 h. Positive SPT (16–57%) and elevated sIgE (19–59%) results were more frequent. Clear-cut positive APT with all SPT and sIgE testing negative was seen in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients. APT, SPT and sIgE results showed significant agreement with history for grass pollen and egg white (two-sided $Pr > |Z| \leq 0.01$). In addition, SPT and sIgE showed significant agreement with history for the other aeroallergens. With regard to clinical history, the APT had a higher specificity (64–91% depending on the allergen) than SPT (50–85%) or sIgE (52–85%). Positive APT were associated with longer duration of eczema flares and showed regional differences. In 10 non-atopic controls, no positive APT reaction was seen.

Conclusion

Aeroallergens and food allergens are able to elicit eczematous skin reactions after epicutaneous application. As no gold standard for aeroallergen provocation in AE exists, the relevance of aeroallergens for AE flares may be evaluated by APT in addition to SPT and sIgE. The data may contribute to the international standardization of the APT.

Introduction

Atopic eczema [atopic dermatitis (AE)] is an inflammatory, chronically relapsing, non-contagious and extremely pruritic skin disease. Atopic sensitization with increased total and specific immunoglobulin E (sIgE) levels is a common finding in patients suffering from AE [for review, see Ref. (1, 2)]. Although the role of allergy in AE is still controversial, some patients with atopic eczema suffer from exacerbation of skin lesions after contact with or inhalation of aeroallergens, e.g. house dust mite (Dermatophagoides pteronyssinus), pollen, animal dander or after ingestion of allergy-inducing foods and improve after appropriate avoidance strategies (3,4). It has been repeatedly shown that in certain patients, eczematous skin lesions can be induced by epicutaneous application of aeroallergens, e.g. house dust mite [for review, see Ref. (5, 6)]. This test procedure, an epicutaneous patch test using allergens shown to induce IgE-mediated sensitizations and the evaluation of an eczematous skin reaction, is called "atopy patch test" (APT) (7). Studies describing experimental patch testing with aeroallergens were published as early as 1937 by Rostenberg and Sulzberger (8) and in 1982 by Mitchell et al. (9); the methods and results used since then have shown wide variations. Potentially irritating procedures like skin abrasion (10, 11), tape stripping (6, 12) and sodium lauryl sulphate application (13) were used to enhance allergen penetration.

For better standardization, we performed APT on non-lesional, non-abraded, untreated skin during remission (7,14). The results were compared for the vehicle and dose of allergen in the preparations used. It was shown that healthy controls and patients with respiratory atopy without a history of eczema do not react to the APT (14) or with a lower frequency and intensity of APT reactions to whole-body mite extract compared with patients with AE (15). Sensitivity and specificity of different diagnostic procedures were calculated in a previous multicenter study (16). Here, we present the results of a prospective European multicenter trial with biologically standardized APT preparations and corresponding allergy diagnosis in 314 patients with AE. This study was designed to define appropriate APT methods, safety aspects and relationship to clinical history of eczema flares using the most common allergens known to elicit reactions in AE patients in Europe. Another aim of the study was to determine the number of individuals with positive APT reactions, but negative sIgE (formerly diagnosed as "intrinsic-type AE") in a larger patient group and to see whether the patients' history to a certain allergen is in agreement with the APT reaction, thus suggesting an important diagnostic role of the APT.

Methods

Patients

After approval by the local ethics committees and obtaining informed, written consent, 314 patients [age range 1.6–80 years; 177 female: mean age 22.6 ± 14.3 years (median 22.09); 137 male: mean age 22.9 ± 17.3 years (median 21.63)] with atopic eczema (1, 2) in actual remission, i.e. in a stable phase without acute flares of eczema, were enrolled in 12 study centers. The group included 76 (24%) children (≤ 10 years). There was no previous selection of patients for prior APT reactivity. using the same standardized documentation forms for test results and clinical history in all study centers, all patients were examined for distribution of (residual) eczematous skin lesions and their history was recorded with regard to atopic diseases, AE duration, previous exacerbations (documentation in forms with regard to every single allergen tested, e.g. for seasonal eczema flares in previous years), previous location of eczema and demographic items. Mean duration of AE was 5.8 ± 5.5 years; 59% had a history of allergic rhinoconjunctivitis, 35% bronchial asthma and 23% urticaria. Before testing, patients were asked whether they experienced eczema flares and itching after contact with house dust or cat. Repeated seasonal variations of eczema severity or sudden, recurrent flares during the birch or grass pollen season (April/May and June to August) were also recorded. In addition, history comprised questions on eczema flares after ingestion of foods with special regard to egg, wheat and celery. 10 healthy, non-atopic volunteers (mean age 26.5 ± 1.2 years, five females) without positive skin-prick test (SPT) or elevated sIgE levels or other signs of atopy were included as controls.

Materials, atopy patch test design and reading

Aeroallergen APT were performed with extracts containing 200 index of reactivity (IR)/g of house dust mite D. pteronyssinus, cat dander, grass and birch pollen allergens in a petrolatum vehicle (Stallergènes, Antony, France). The potency of 100 IR was designated as the strength of allergenic extract that elicited a geometric mean wheal diameter of 7 mm on SPT in 30 subjects sensitive to the corresponding allergen. Major allergen contents (only available for aeroallergens) are given in Table 1. Extracts of egg white, wheat flour and celery were tested and standardized for protein content in petrolatum and protein contents are also shown in Table 1. After discontinuation of antihistamines, and systemic and topical steroids for at least 5 days, the test substances were applied in a randomized, double-blind design for 48 h in Large Finn Chambers (diameter 12 mm; Epitest Ltd, Oy, Finland) on clinically uninvolved, not pretreated back skin. All reactions were evaluated after 24 reapplied), 48 and 72 h and compared with simultaneously performed

corresponding SPT (Stallergènes), and specific sIgE [CAP-radioallergosorbent test (RAST)-flurescence enzyme immunoassay; Pharmacia, Uppsala, Sweden] as classical methods for diagnosing type I sensitizations. Grading of positive APT reactions was similar to the criteria used in conventional contact allergy patch testing [International Contact Dermatitis Research Group (ICDRG) rules] with the modifications of the European Task Force on Atopic Dermatitis (ETFAD) Consensus Meetings (17); i.e. -, negative result; ?, only erythema, questionable; +, erythema, infiltration; ++, erythema, few papules (up to 3); +++, erythema, papules from 4 to < many; ++++, erythema, many or spreading papules; +++++, erythema, vesicles. A patch test with the pure vehicle served as negative control.

Major allergen concentrations in the extracts (200 IR/g) (μg/ml) (ELISA)	
House dust mite	
Der p 1	59
Der p 2	6
Cat Dander	
Fel d 1	9
Grass pollen	
Phl p 1	2
Birch pollen	
Bet v 1	165
Protein concentrations (μg/ml) (Bradford Method)	
House dust mite	98
Cat dander	75
Grass pollen	132
Birch pollen	334
Wheat	158
Celery	44
Egg white	740

Table 1
APT material: allergen and total protein content. Vehicle: petrolatum. For food patch test preparations, only standardized protein content was available.

All investigators participated in pre-study standardized test reading sessions. Test application and reading were performed by different investigators. Thus, reading of reactions was performed by an investigator without the knowledge of the (control) test sites or patient's history. Only reactions from + (i.e. erythema, infiltration) onwards were designated clear-cut positive. The APT procedure in this study was performed in the same way as in our previous studies on AE patients and healthy controls (14, 16).

Statistics

Statistical analysis of the data was performed with SPSS®-Software using chi-square and linear association tests. After checking for normal distribution, paired t-test was used to compare mean rates of positive APT reactions, SPT and elevated sIgE in the study centers. Multivariate analysis was performed using a logistic regression model of APT outcome predictors.

Results

Patients' history of exacerbation after allergen contact/ingestion

10–39% of the patients reported eczema exacerbations after aeroallergen contact, mostly to house dust mite. Seasonal flares were reported in 17%. Food allergens were suspected in 1–7% of this mostly adult population. Table 2 shows the history in comparison with other clinical variables.

Allergen	SPT	sIGE	APT	History	Concordance
Dermatophagoides pteronyssinus	56	56	39	34	57
Birch pollen	49	53	17	20	61
Grass pollen	57	59	15	31	64
Cat dander	44	46	10	30	62
Egg white	25	19	11	7	77
Wheat flower	16	38	10	3	78
Celery	20	30	9	1	79

Table 2
Positive test results and patients' history of allergen associated eczema flare. All values are percentage values. Frequency of positive APT reactions is lower than that of positive IgE-mediate sensitizations. Patients' allergen specific history of eczema flares after allergen exposure was obtained prospectively. Concordance refers to APT and history.
N=314, 24% children ≤ 10 years.
SPT, skin prick test ≥ 3 mm; sIgE, specific IgE ≥ 0.35 kU/l; APT, atopy patch test ≥ +.

Eczema pattern

A total of 113 of the 314 patients (37%) reported skin lesions only in areas not covered by clothing and therefore a predictive eczema pattern for aeroallergen contact: the neck, face and scalp, hands and arms (over the last 12 months).

Skin-prick test and specific IgE

The frequencies of positive test results are given in Table 2. Concerning one allergen, the frequencies of SPT and sIgE, the classical tests of IgE-mediated hypersensitivity, were very similar to each other (except for wheat flour) and always higher compared with the frequency of a predictive history or positive APT. SPT reactions with a wheal diameter <3 mm were regarded as negative.

Atopy patch test

All tested allergen preparations were able to elicit positive, clear-cut eczematous reactions in subgroups of patients, but not in control subjects. Positive reaction to the vehicle control area was only seen in three of 302 patients (0.99%). The frequency of the positive APT reactions is also given in Table 2. Whereas food allergens elicited positive reactions in the investigated population in about 10%, the most frequent allergen causing positive APT was D. pteronyssinus (39%), followed by pollen allergens. An example of a positive APT reaction is shown in Fig. 1. Higher frequencies of positive APT reactions to food allergens were seen in children compared with adults (wheat flour: 15% vs 8%; celery: 12% vs 8%) except for egg white (both 11%).

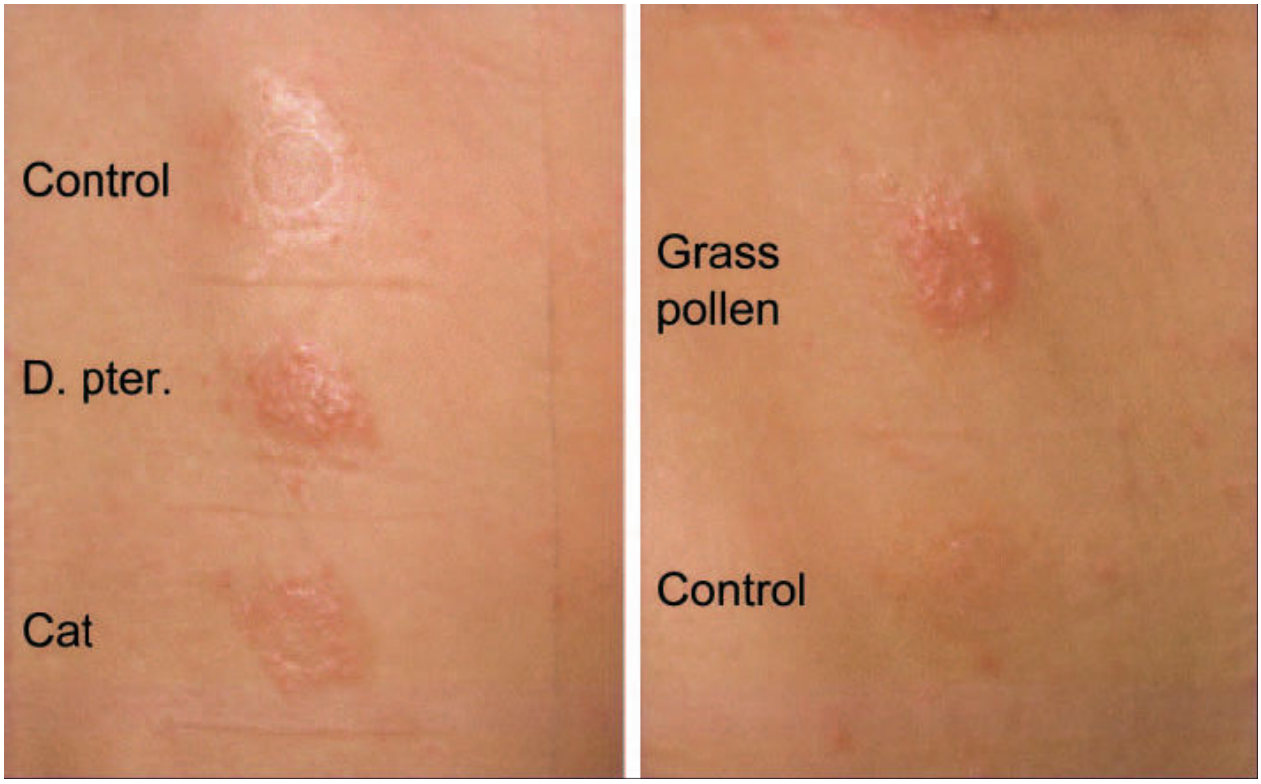

Figure 1
APT reactions to different allergens after removal of Finn Chambers after 48 h. Clear-cut eczematous appearance with infiltration and spreading papules, partially with a follicular pattern. Control: petrolatum.

The reactions to D. *pteronyssinus* are given in Fig. 2 with regard to their frequency at different timepoints and their intensity distribution. The results of other allergens are distributed similarly (not shown). Figure 2 also demonstrates, as an example, that at 24 h after application, only very few positive reactions were seen. Evaluations of APT after 48 and 72 h gave more frequently clear-cut positive reactions than after 24 h. Using the differentiated reading key of the ETFAD, the intensity of positive APT reactions is distributed similar to a logarithmic normal distribution.

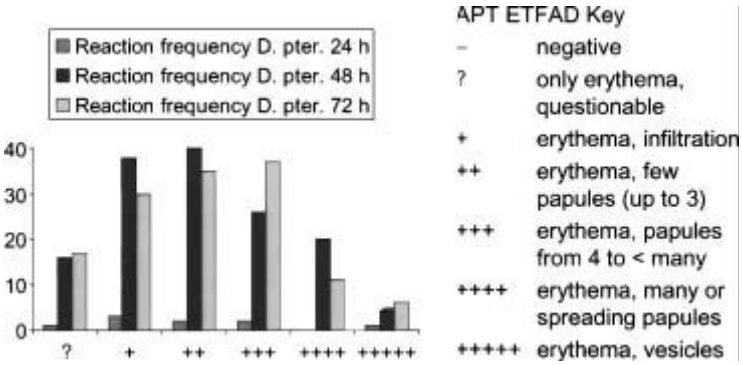

Figure 2
APT ETFAD grading: reaction frequencies of different intensities and time points. Distribution of patients with different APT reading key units according to ETFAD Consensus Meetings (17) for the most frequent allergen, house dust mite (*D. pteronyssinus*). After 24 h, positive APT reactions were rare. APT reading after 48 and 72 h is recommended (n=314).

Agreement analysis: history, skin prick test, specific IgE, eczema pattern

For grass pollen and egg white, APT, SPT and sIgE results showed significant concordance with a prospectively obtained predictive history of eczema exacerbations (two-sided $Pr>|Z| \leq 0.01$). In addition, SPT and sIgE showed significant agreement with history for the other aeroallergens. In 83% of patients, corresponding SPT or sIgE results were found to match with the individual positive APT. A subgroup of patients was characterized by negative SPT and sIgE, but clear-cut positive APT results. There were 22 patients (7%) with clear-cut positive APT but without any positive SPT or elevated sIgE to all the allergens in the panel. With regard to a single APT-positive allergen, this was seen in 53 (17%) of the patients. No significant difference in the agreement with history was seen when comparing these patients with the IgE-positive group. The distribution of allergens is shown in Fig. 3.

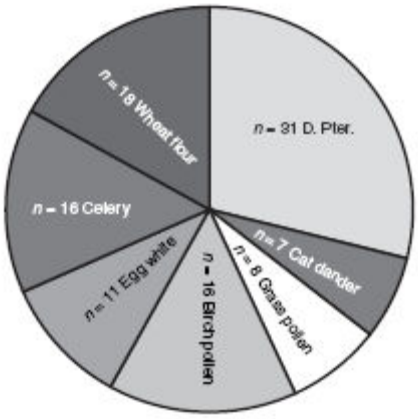

Figure 3

- Observed in 53 of 314 patients (17%)
- N=22 APT+, but no positive SPT or sIgE at all (7%)

Patient subgroup with at least one positive APT reaction without corresponding skin-prick test / specific IgE. Clear-cut positive APT with all SPT and sIgE tested negative was seen in 7% of the patients, whereas a positive APT without SPT or sIgE for the respective allergen was seen in 17% of the patients

No significant association between air-exposed eczema distribution pattern and a positive APT result was seen ($P > 0.05$, n=188). The duration of the last eczema flare in patients with at least one allergen with positive APT reaction (n=84) was 186 ± 380 days (median 105 days). In patients with negative APT (n=104), the duration was shorter: 143 ± 278 days (median 82 days; difference not significant, $P > 0.05$).

	Sensitivity			Specificity		
Test	SPT	sIgE	APT	SPT	sIgE	APT
Dermatophagoides pteronyssinus	68*	72*	45	50*	53*	64
Cat dander	79*	80*	14	71*	69*	91
Grass pollen	80*	84*	28*	54*	53*	91*
Birch pollen	69*	73*	15	57*	52*	83
Egg white	68*	59*	32*	78*	85*	91*
Celery	100*	50	33	81*	71	91
Wheat flower	30*	78	30	85*	63*	91

Table 3.

Sensitivity and specificity of different test procedures with regard to patients' history. All values are percentage values. Referring to predictive history of eczema exacerbations in pollen season, in direct contact with allergen, or after food ingestion (n=314).

* Agreement with history (two-sided $Pr>|Z| \leq 0.01$).

The APT shows a higher specificity than classical tests for IgE-mediated hypersensitivity with regard to the allergen-specific history.

Sensitivity and specificity of different test procedures

The accuracy parameters sensitivity and specificity were calculated for all allergens and compared with the classic tests of IgE-mediated hypersensitivity (Table 3). The criteria for a "true positive" test was, as usual in epicutaneous testing, a corresponding predictive history of the patient with the investigated allergen. It could be demonstrated in all tested allergens, that the specificity of the APT was always higher than the specificity of SPT or RAST. However, the sensitivity was lower, depending on the allergen studied.

Regional differences of APT reactivity

Table 4 shows the mean percentages of patients with positive APT reactions to the four tested aeroallergens, in comparison with different countries. Marked differences were seen in these numbers, especially for the seasonal pollen allergens and for cat dander. Less positive reactions to pollen were obtained in Switzerland, France and Italy compared with the Netherlands, Belgium and Germany. No significant regional differences were observed for food allergens (not shown). Comparing the percentual frequencies of positive APT and corresponding elevated allergen-specific serum IgE per center, a paired t-test analysis showed significant association of these parameters for cat, grass and birch pollen.

	Allergen			
Country	*Dermatophagoides pteronyssinus*	Cat*	GP*	BP*
The Netherlands (n=36, 2 centers)	42	3	16	22
Belgium (n=32, 2 centers)	44	13	8	19
Germany (n=162, 4 centers)[1]	36	11	20	21
Switzerland (n=42, 2 centers)	40	5	5	2
France (n=9, 1 center)[2]	67	11	0	11
Italy (n=30, 1 center)	17	10	7	7

Table 4
Percentage of positive APT per allergen per country. All values are percentage values. Regional differences of APT reactions were seen.
[1] Including German Clinic in Davos, Switzerland.
[2] Pediatric study center.
* Association of APT with specific IgE, $p < 0.05$

Adverse events

In 25 of 314 patients (7.7%), adverse side-effects were reported, described as local eczema flares, contact urticaria, irritation caused by adhesives, and itching in test sites, some of which required topical therapy. One event was graded as severe, where a patient developed breathing problems in the night following APT and SPT. After removing of the APT and a lung X-ray, the patient recovered. A causal relation to the APT was unlikely.

Discussion

This is the first international multicenter study describing the feasibility of APT in a clinical setting with a controlled, double-blind design. The results of this study confirm that aeroallergens and food allergens are able to elicit eczematous skin lesions in a number of patients with atopic eczema when applied epicutaneously on untreated skin. The methodology used, in contrast to many experimental models for APT, is suitable for allergological routine, can be standardized across many sites, and can be interpreted on a clinical background in patients with atopic eczema.

As a "gold standard" of aeroallergen provocation test in atopic eczema does not exist, the individual allergen-specific history of previous eczema exacerbations was used like in conventional contact allergy testing as a substitute for a relevance parameter. For aeroallergens, patient's history has previously been shown to be suitable to evaluate clinical relevance, especially for seasonal allergens (16, 17). Food provocation challenges were not included as no international standardization was achieved a priori and feasibility is large-scaled. In this study, significant associations of APT results with the prospectively obtained history were seen with exposure to grass pollen as seasonal allergen and egg white as most frequent food allergen.

Atopy patch test evaluation after 48 and 72 h gave the number of positive APT results; however, after 24 h no relevant results could be obtained. The two later reading timepoints should be considered relevant in patch testing with aeroallergens; Fig. 2 shows a 10% higher frequency at 48 h compared with 72 h, for most positive APT key units. In addition, the distribution of APT reading key units in this multicenter study indicates the suitability of the ETFAD key for clinical routine. The cutoff of a positive APT reaction needing to be at least infiltrated (not only erythema) has previously been used successfully (14, 16); a visual score was recently shown to be superior in differentiation between irritative and allergic reactions compared with chromametry and laser Doppler imaging (18).

The sensitivity analysis, in comparison with previous studies (16, 17), suggests that for some allergens APT allergen concentrations >200 IR/g may be necessary to demonstrate a sensitization. Further studies with larger numbers of (pediatric) patients and including food challenges are necessary for food allergens, after better standardization of the allergen content. Celery was included as a known cross-allergen in adults (age >10 years in 76% of the study group) and indeed the number of patients with a positive APT to celery is markedly higher than the number of patients with a history of celery-associated eczema flares (Table 2). As a result of the overall low reactivity to celery APT and the lack of food provocation, these associations should be interpreted cautiously. Milk as a relevant food

allergen in children could not be produced in a standardized APT preparation for this study. Higher numbers for sensitivity and specificity of APT with unprocessed native food were reported by Niggemann et al. (19) and Roehr et al. (20), using food provocation outcomes as calculation basis.

The regional subgroup analysis of this international multicenter study showed wide variations in the rate of positive APT reactions in spite of the highly standardized test procedure. This observation may partially explain the different outcomes of previous APT studies from different countries. Differences in patients' sensitization rates, probably due to different allergen exposure to certain aeroallergens may be one reason for this variation. This hypothesis is sustained by the significant association of the APT positivity rate and the corresponding specific IgE in the centers, arguing against investigator bias in APT reading (which was also standardized in training sessions).

The association of positive APT with specific IgE to certain allergens in this study suggests the role of allergenspecific IgE in the development of eczematous skin lesions after allergen contact in this study and confirms previous results (16). Mite allergen in the epidermis under natural conditions (21) as well as in APT sites (10, 13) has been demonstrated in proximity to Langerhans cells. Langerhans cells in the skin express IgE receptors of three different classes (22–24). In addition, a Birbeck granule negative, non-Langerhans cell population with an even higher IgE-receptor expression than the Langerhans cell, the so-called inflammatory dendritic epidermal cell (IDEC), has recently been demonstrated in freshly induced APT lesions (25, 26), a phenomenon which occurred in both "intrinsic" and "extrinsic" patients (26). This might explain IgE-associated activation of allergenspecific T cells finally leading to eczematous skin lesions in the APT (27, 28). According to the results of Langeveld-Wildschut et al. (29) the positive APT reaction requires the presence of epidermal IgE+ CD1a+ cells.

That classical IgE-mediated tests like SPT and the proof of sIgE by CAP-RAST show positive reactions in the majority of patients with AE (1, 5, 14, 18), could also be demonstrated in this study. However, these tests are of low specificity. In contrast, the APT was associated with the more specific information, which patient really experienced deterioration of AE after aeroallergen contact. Therefore, the outcome of APT can only partially be predicted by sIgE, SPT or history, which, alone or in combination, can only be a substitute for the specific provocation or allergen avoidance measures. The very low frequency of reactions to vehicle control tests and the high number of positive reactions to allergen-carrying test substances in this study demonstrates the advantage of an APT method without irritating procedures like tape stripping or abrading to enhance allergen penetration.

In some patients with negative SPT with or without sIgE, clear-cut positive APT reactions were observed. It is well known that SPT and sIgE are not perfectly concordant when compared in a larger group of patients, since they may indicate sensitization in different compartments of the body (i.e. IgE on skin mast cells or in the serum). In contrast to SPT and sIgE, the APT gives additional information on another pathophysiological aspect, eczematous skin inflammation.

In summary, APT is not proposed as a single screening test in patients with atopic eczema. It may rather be used in addition to SPT and sIgE as a tool to prove clinical relevance of a given sensitization. A sensitization detected by APT, which is supposedly T-cell mediated, may be even more relevant for the clinical course of atopic eczema than the demonstration of an IgE-mediated sensitization. However, without the clear-cut positive APT, 7% of the tested patients who would be labelled as "intrinsic type" of atopic eczema according to Wüthrich's definition (30), show a sensitization in the APT. A similar finding of positive APT reactions in subjects without sIgE to Dermatophagoides was described by Seidenari et al. (31) and Manzini et al. (32). Moreover, recently eight of 12 "intrinsic" atopic eczema patients were reported to react to a partially purified whole-mite APT preparation by Ingordo et al. (33). Similar results have been obtained by APT with Malassezia sympodialis antigen (34). House dust mite-specific antibodies of the IgG4 subtype, as well as a rapid influx of IDEC in the APT lesions has recently been reported in two otherwise "intrinsic" atopic eczema patients (35). However, the mechanism of these "intrinsic" APT reactions remains hypothetical to date, but a T-cell mediated mechanism without IgE involvement seems probable. With regard to the recently proposed novel nomenclature for allergy by the European Academy of Allergy and Clinical Immunology (36), these cases may be diagnosed as "non-IgE-associated AEDS" or "T-cell-mediated AEDS", respectively.

The APT model used in this study with standardization of allergen concentration and vehicle may provide an important diagnostic tool to select those patients who show special benefit from allergen avoidance procedures or allergen-specific immunotherapy (37). To date, there are no data from intervention studies supporting that patients with positive APT benefit from allergen avoidance (38, 39). The APT with allergens in petrolatum may be used in the future as a kind of provocation test on the skin, but food challenge tests as gold standard in food allergic patients with AE are not replaced. The APT may even identify those patients with negative SPT and sIgE. However, the clinical relevance of positive APT reactions is still to be proven by standardized provocation and avoidance tests and may also depend on the APT model used and outcome definitions.

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Delayed and immediate type reactions in the atopy patch test with food allergens in young children with atopic dermatitis.

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In recent years the Atopy Patch Test (APT) has been suggested as an addition in the allergologic work-up of children with AD and suspected food allergy. We initiated a prospective clinical study in children with atopic dermatitis (AD) younger than 3 years, to evaluate the additional clinical value of the atopy patch test (APT) next to our own standardized allergologic work-up in case of a suspected food allergy.

One hundred and thirty-five children were included in the study. They were tested using the skin application food test (SAFT), the APT and measurement of specific IgE. The allergens used in the skin tests were freshly prepared food stuffs and included commercially available cow's milk (CM), the egg white of a hard boiled hen's egg and mashed peanuts in a saline solution. Allergy was defined using a flow-chart incorporating the results from the SAFT, oral challenges (OCs) and elimination and (re)introduction periods. To determine the additional value of the APT next to the SAFT, we analyzed the SAFT negative patients per allergen and used an exact binary logistic analysis to evaluate the simultaneous effects of the APT and measurement of specific IgE, calculating mutually adjusted odds ratios (OR's) for positive APT's and specific IgE levels above 0.70 U/l.

We found clinically relevant food allergies in 23% (egg white) to 28% (cow's milk and peanut) of our study population. Positive SAFT reactions were observed in 14% (peanut), 16% (egg white) and 21% (cow's milk) of our patient population. Next to the SAFT we did not observe a significant additional value of the APT for the diagnosis of cow's milk or egg white allergy, but we did find a significant additional value for the diagnosis of peanut allergy (OR 11.56; $p<0.005$, 2-sided). In clinical practice this statistically significant value does not exclude the need for OC and controlled elimination and (re)introduction periods due to the presence of false negative as well as false positive results in the APT.

In conclusion we could not find enough support for the current addition of the APT to our standardized allergologic work-up in young children below the age of three years with AD and suspected food allergy. At the moment the additional value of the classical delayed type APT next to the SAFT seems to be very limited at best in this study population and does not justify the time consuming nature of the skin test.

Introduction

Atopic dermatitis is a chronic multifactor inflammatory skin disease with a genetic background. It is part of the so-called atopic syndrome and may be associated with a sensibilisation for food allergens, especially in childhood. Although the clinical relevance of this sensibilisation is not always clear, there is a small sub-population of children with AD who do develop clinically relevant reactions to different food allergens. This group may benefit from dietary measurements and needs to be separated from the majority of children with AD in whom diets are not beneficial.

The allergologic work-up in children with AD and suspected food allergy starts with a careful history and clinical examination. Additional tests usually include the Skin Prick Test (SPT) and/or measurement of serum specific IgE, both aimed at revealing immediate type sensibilisation against the allergens tested. The Skin Application Food Test (SAFT) has been described as a reliable and child friendly alternative to the SPT in children with AD below the age of 3 years.[1] The gold standard for the diagnosis of a food allergy is still an oral challenge (OC), preferably double blind placebo controlled and followed by a supervised reintroduction period.[2] Although OC are time-consuming and carry a certain risk, they may be necessary in cases were serology, skin tests and history do not reveal a conclusive result.

In recent years the Atopy Patch Test (APT) has been suggested as an addition in the allergologic work-up of children with AD and suspected food allergy.[3,4,5] The APT is aimed at detecting delayed type, eczematous, allergic reactions to allergens commonly associated with direct type, IgE mediated, allergic reactions. It's addition is advocated as a means to reduce the number of OC necessary in order to reach a conclusive result.[6,7] Although in theory the combination of a skin test aimed at immediate type allergic reactions (SPT or SAFT) and a skin test aimed at delayed type allergic reactions (APT) seems promising, there have been conflicting results published regarding the clinical value of the APT in daily practice.[3-10]

We initiated a prospective clinical study in children with AD younger than 3 years, to evaluate the additional clinical value of the APT next to our own standardized allergologic work-up in case of a suspected food allergy.

Materials and Methods

The study was performed on the paediatric dermatology out-patient clinic of the Erasmus MC-Sophia Children's Hospital. Children aged 0-3 years with AD and an indication for an allergologic work-up, were eligible for inclusion. AD was defined by the criteria of Williams et al.[11] Indications for an allergologic work-up consisted of suspected food

allergies due to reported reactions, pre-existing diets or refractory skin disease. The inclusion period lasted 2 years and 10 months.

Patients were subjected to our standardized work-up consisting of a careful history, focusing on clinical signs of food-allergy, combined with the SAFT and measurement of specific IgE. The allergens used in the skin test were freshly prepared food stuffs and included commercially available cow's milk (CM), the egg white of a hard boiled hen's egg and mashed peanuts in a saline solution. There was no further dilution of the allergens and the foodstuffs were tested in the form in which they would be eaten. In addition the APT was performed, using the same allergens as were used in the SAFT.

Skin Application Food Test

SAFT were performed on the unabraded volar aspects of the lower and if necessary upper arm, using medium (8 mm) Finn-chambers on scanpor. A saline solution was used as a negative control. They were read after 10, 20 and 30 minutes. The skin test was removed after 30 minutes or earlier if an urticarial weal and flare response occurred during the prior reading times. Evaluation took place using a scale from 0-3 with 0 indicating no reaction, 1+ erythema only, 2+ urticarial weals within the test area and 3+ urticarial weals spreading beyond the test area. Only 2+ and 3+ reactions were regarded as positive.[1]

Atopy Patch Tests

APT were performed on the unabraded skin of the back using large (12 mm) Finn-chambers on scanpor. A saline solution was tested as a negative control. If the above mentioned SAFT test was positive the APT was removed. After 20-30 minutes the remaining test areas were examined as well, to make sure there was no urticarial weal and flare reaction, in which case the skin test would also be removed. Subsequently the Finn chambers were covered with fixomull, to prevent them from shifting. The skin tests were removed after 24 hours, because we feared possible putrefication of the fresh foods might lead to false positive results. The APT was evaluated after 48 and 72 hours, using the guidelines described by the European Taskforce on Atopic Dermatitis (ETFAD).[12] Only clear-cut reactions of 2+ or more were regarded as positive.

Specific IgE

Blood was drawn from each patient. Allergen-specific IgE was measured in serum with the CAP system (Pharmacia, Woerden, The Netherlands) according to the manufacturer's instructions. Only levels of 0,70 U/l or more were regarded as positive.

Definition of allergy for this study

Figure 1 shows the flow chart used to identify a relevant allergy for any of the three food stuffs. The first step in this chart is based on the results from the SAFT, which has shown a positive predictive value of 100%, as our study group reported previously.[1]

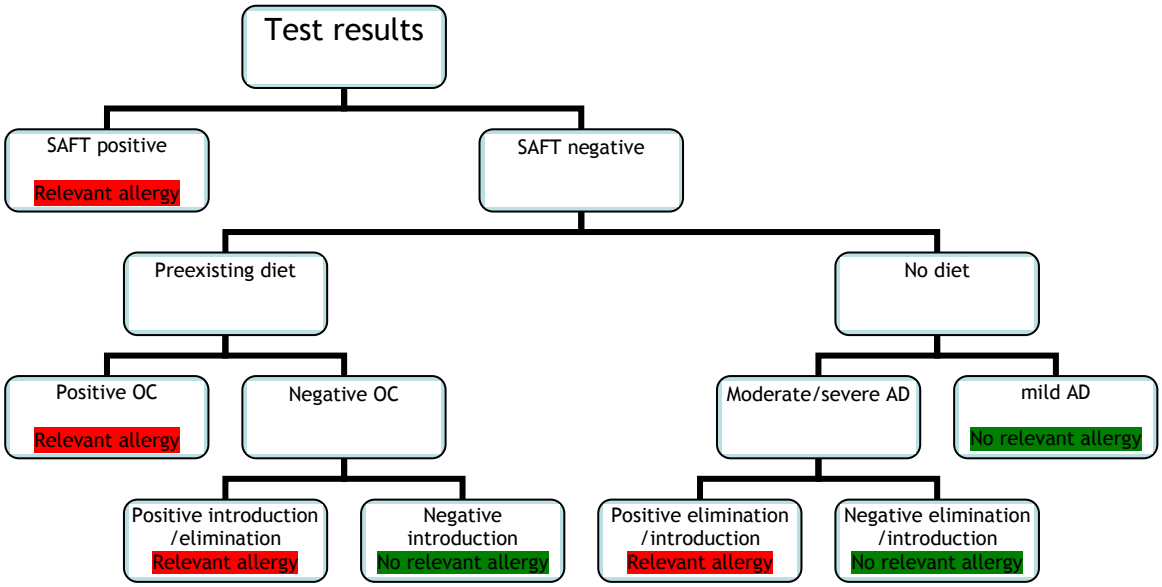

Figure 1
Flow-chart used to identify a relevant allergy in our study population. SAFT=skin application food test; APT=atopy patch test; AD=atopic dermatitis; OC=oral challenge.

Oral challengens

Oral challenges (OC) were performed in our day-care unit. Below the age of two years we generally performed the OC open. When specific IgE levels were above 0,70 U/l they were performed giving the suspected food stuffs in 5 steps with a slowly increasing dose and 1 hour between each step. The total duration of the OC was 8 hours. Safety measures included a capped off infusion needle inserted in an arm vein before the start of the OC. Adequately dosed clemastine, epinephrine and hydrocortison infusion fluids were prepared based on the weight of the patient. When specific IgE values were below 0,70 U/l the total duration of the OC was shortened and the suspected food stuff was given in 3 steps with a more rapidly increasing dosage and 15 minutes between each step (bulk provocation). Adequately dosed medication as described above was prepared but the infusion needle was not inserted. A qualified paediatric nurse was present during the entire duration of the challenges. After a negative oral challenge a monitored introduction period of 4-6 weeks was initiated (see below)

Food elimination and (re)introduction

Elimination and/or introduction periods for a single food allergen lasted 4-6 weeks. Before and after each episode an evaluation by a research physician took place. Parents were educated and monitored by a qualified dietician with experience in paediatric patients with food allergies.

Ethical aspects and statistical analysis

The study was approved by the Medical Ethics Committee of the Erasmus MC. The parents of all patients signed informed consent. The statistical analysis was performed using SPSS version 11.0 and LogXact version 4.1.

Results

One hundred and forty eight children were eligible for inclusion. We experienced 13 dropouts due to active skin disease on the test areas (n=8), very strong positive dermography (n=1), multiple positive APT reactions, including the negative control (angry back, n=3) and 1 child who developed fever based on an airway infection during the test week. The remaining 135 children included 33 children below the age of 1 year and 102 children between 1 and 3 years of age.

We were unable to collect complete data concerning the presence of allergy in 34 patients representing 50 APT tests. This was mainly caused by failure to complete the process of OC and/or elimination and (re)introduction in a timely manner because of parents refusing an OC (n=14) or loss during follow up (n=17). Reasons for refusing an OC consisted of anxiety concerning the OC procedure, especially placement of the infusion needle or the wish to continue the diet anyway due to believed preventive properties of the diet or the presence of family members with an allergy already making a "family diet" necessary. One patient suffered from a concomitant gastro-intestinal disorder other than food allergy and needed continuation of hypoallergenic milk substitution and two patients had their OC cancelled due to the failed insertion of an infusion needle and an exacerbation of AD prior to the OC respectively.

	SAFT		APT		Additionally diagnosed allergy	
	Positive	**Negative**	**Positive**	**Negative**	**Positive**	**Negative**
Cow's milk	26 (n=125)	99 (n=125)	7 (n=99)	92 (n=99)	9 (n=99)	90 (n=99)
Egg white	19 (n=120)	101 (n=120)	11 (n=101)	90 (n=101)	7 (n=101)	94 (n=101)
Peanut	15 (n=110)	95 (n=110)	18 (n=95)	77 (n=95)	15 n=95)	80 (n=95)

Table 1
Number of positive and negative Skin Application Food Tests (SAFT), Atopy Patch Tests (APT) and Additionally diagnosed allergy. APT were only performed in SAFT negative patients. The additional diagnosis of food allergy was made in SAFT negative patients using oral challenges and elimination/reintroduction periods as defined in the flow chart in fig. 1.

Cow's milk

In 10 patients the data concerning allergy was incomplete. The remaining 125 patients included 26 patients (21%) with a positive SAFT reaction. Nine additional patients (7%) were later diagnosed with food allergy and 90 patients (72%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test there seemed to be a significant additional value of the APT in proving the diagnosis cow's milk allergy in the SAFT negative patient group (p=0.015, 2-sided). Likewise the presence of specific IgE also showed a significant additional value (p=0.014, 2-sided). We used exact binary logistic regression analysis to evaluate the simultaneous effects of the APT and specific IgE (Table 2). The mutually adjusted odds ratios (OR's) for a positive APT and specific IgE above 0.70 U/l are 9.61 and 5.58 respectively. However, the OR of the APT, adjusted for specific IgE, is not significant (p=0.051, 2-sided) and the OR of specific IgE, adjusted for the APT, is only borderline significant (p=0.047, 2-sided).

	Odds ratio	95% CI		p-value (2-sided)
		lower	upper	
Cow's milk				
APT	9.61	0.99	95.52	0.051
IgE	5.58	1.02	39.06	0.047
Egg white				
APT	1.05	0.02	11.60	1.000
IgE	10.37	1.49	∞	0.014
Peanut				
APT	11.56	2.10	87.75	<0.005
IgE	32.86	4.94	∞	<0.005

Table 2
Exact binary logistic regression model listing the odd ratios for allergy in case of a positive atopy patch test or specific IgE value in patients with a negative SAFT, given the combination of both tests. CI=confidence interval; APT=atopy patch test

Egg white

In 15 patients the data concerning allergy was incomplete. The remaining 120 patients included 19 patients (16%) with a positive SAFT reaction. Seven additional patients (6%) were later diagnosed with food allergy and 94 patients (78%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test we found no significant additional value of the APT in proving the diagnosis egg white allergy in the SAFT negative patient group (p=0.566, 2-sided). However, the presence of specific IgE did show a significant additional value (p=0.013, 2-sided). In the exact binary logistic regression analysis the respective OR's are 1.05 and 10.37 (Table 2). The OR of the APT, adjusted for specific IgE, is very near 1 and off course not significant (p=1.000, 2-sided). The OR of specific IgE, adjusted for the APT, equals 10.37 and is significant (0.014, 2-sided).

Peanut

In 25 patients the data concerning allergy was incomplete. The remaining 110 patients included 15 patients (14%) with a positive SAFT reaction. 15 additional patients (14%) were later diagnosed with food allergy and 80 patients (72%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test we found an additional value for both the APT and specific IgE in proving the diagnosis peanut allergy in the SAFT negative patient group (both p<0.005, 2-sided). In the exact binary logistic regression analysis the respective mutually adjusted OR's are 11.56 and 32.86, both significant (Table 2: p<0.005, 2-sided).

Discussion

The APT could form a relevant and important addition to our allergologic work-up of patients with AD and a suspected food allergy. We know from previous research that the delayed type skin reaction in a positive APT is allergen specific, correlates with the presence of food allergy, is predominantly if not only observed in patients with AD and forms an in-vivo model of the skin lesions in AD.[10] Combining skin tests aimed at immediate type allergic reactions, like the SPT or SAFT, with a skin test like the APT could be very beneficial. However, previously reported results regarding the additional value of the APT in the diagnosis of food allergy in children with AD are very variable. Reported sensitivity ranges from 18% to 93%, specificity from 41% to 97% and positive predictive values from 40% to 96%.[3-10] Some authors claim a reduced need for OC, especially when APT and SPT or specific IgE values are combined.[6,7] Others are less enthusiastic about the value of the APT in daily clinical practice.[8,9] Comparing the data from these studies is difficult due to

varying patient populations, differences in methodology and interpretation of skin testing and differences in methodology and interpretation of OC, including the presence of subdivisions in early and late allergic reactions. The first steps towards standardization have been made, but further work is still needed.[10,13-15]

Our study was initiated to determine the additional value of the APT in our standardized allergological work-up of young children below the age of 3 years with AD and suspected food allergy. Our usual work-up in this age group consists of the SAFT and measurement of specific IgE with additional OC and elimination and (re)introduction periods if necessary. We wanted to know if the APT could identify children with a false negative SAFT, thus reducing our need for oral challenges and/or elimination and (re)introduction periods. To determine the additional value of the APT next to the SAFT, we analyzed the SAFT negative patients per allergen and used an exact binary logistic analysis to evaluate the simultaneous effects of the APT and measurement of specific IgE, calculating mutually adjusted OR's for positive APT's and specific IgE levels above 0.70 U/l. The results showed clinically relevant food allergies in 23% (egg white) to 28% (cow's milk and peanut) of our study population. Next to the SAFT we did not observe a significant additional value of the APT for the diagnosis of cow's milk or egg white allergy, but we did find a significant additional value for the diagnosis of peanut allergy (OR 11.56; $p<0.005$, 2-sided). In clinical practice this statistically significant value does not exclude the need for OC and controlled elimination and (re)introduction periods due to the presence of false negative as well as false positive results in the APT. This concurs with the conclusions of Mehl et al, who found that in daily clinical practice the APT adds only a small predictive value to the standard SPT and sIgE measurement in the diagnostic work-up of suspected food allergy in children.[16]

When we looked at the presence of specific IgE concentrations above 0.70 U/l, there was a significant additional value for this measurement next to the SAFT for diagnosing an allergy for peanut (OR 32.86), egg white (OR 10.37) and cow's milk (OR 5.58). However, there were false negative and especially false positive values present, resulting in the need for continued OC and controlled elimination and (re)introduction periods. This is in concordance with what we know from the literature regarding the use of elevated levels of food-specific IgE as a test for clinically relevant food allergy.[12] Especially the presence of false positive values but also the presence of false negative values warrants caution in the interpretation of this test. The group from Sampson was the first to report improved results by using food-specific IgE concentrations that could predict clinically relevant food allergy with more than 95% certainty in their study population.[17,18] Although others have reported similar results we have not been able to determine comparable 95% predictive

values in our own setting due to a wide variation in specific IgE levels in patients with and without a clinically relevant allergy [Novak J and Oranje AP, abstract ESPD congress 2005].

Because the methodology of the SAFT and APT basically only differ with regard to occlusion and reading time we would expect a substantial number of urticarial reactions during an APT with food allergens. We also know from experience that a strong positive SAFT can be followed by a positive delayed type eczematous reaction after 2-3 days, even if the allergen is removed after 20-30 minutes [unpublished data]. We found positive SAFT reactions in 14% (peanut), 16% (egg white) and 21% (cow's milk) of our patient population. However, data on the occurrence of urticarial APT reactions to food allergens is almost non-existent and if reported seems to consist of relatively low percentages.[3-9,15,16] We suspect urticarial APT reactions are relatively underreported. This might be caused by a lack of inspection of the test site after 20-30 minutes. Differences in study populations may also play a part, as we know that contact urticaria to food allergens are predominantly found in younger children.[19] In our own study population the question remains whether some or all positive SAFT reactions in our study would have turned out as positive APT reactions if they had not been removed. For future use we would like to propose to change the name of the SAFT into the immediate type APT reaction. With this name change we hope to prompt increased interest in the urticarial immediate type reactions which can be found next to the classical delayed type APT reaction, especially in young children with AD and food allergy.

Our study took place in a clinical setting and is based on a large number of young children with AD. The drop-outs during inclusion (n=13) and the incomplete data on allergy (n=34 representing 50 APT tests) could in theory encompass a bias for the presence of allergy. However, based on the reasons why the data was not available and the fact that patient characteristics between patients included and excluded for statistical analysis are very similar, such a bias is not to be expected.

In conclusion we could not find enough support for the current addition of the APT to our standardized allergologic work-up in young children below the age of three years with AD and suspected food allergy. At the moment the additional value of the classical delayed type APT next to the immediate type APT (or SAFT) seems to be very limited at best in this study population and does not justify the time consuming nature of the skin test. This conclusion is supported by a recent publication from Mehl et al.[16] Further studies aimed at standardization, reproducibility and clinical validation are needed before the APT with food allergens can be used in routine daily clinical practice as a diagnostic test. Despite our current findings we believe these studies are worthwhile to undertake because a

positive APT with food allergens does function as an allergen specific delayed type hypersensitivity reaction, which still seems promising for further use as a diagnostic test.

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Atopy patch tests with aeroallergens in children aged 0-3 years with atopic dermatitis

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Background

Epicutaneous application of aeroallergens is able to elicit eczematous skin reactions in patients with AD. Most of the current clinical data on this so-called Atopy Patch Test (APT) with aeroallergens is based on adult patient populations and pediatric data is scarce.

Aims of the study

Evaluation of the presence of positive APT and their correlation with elevated levels of serum specific IgE and/or the presence of positive Skin Prick Tests (SPT) in children with AD up to 3 years of age.

Methods

Children eligible for inclusion were submitted to a careful history, the APT and measurement of serum specific IgE. In children older than 1 year of age additional SPT were performed. Investigated allergens included dog dander, cat dander and house dust mite.

Results

We included 135 children, with an age distribution ranging from 5 to 35 months. There were 51 girls and 84 boys. Positive APT reactions were found in 12.5% to 25% of patients. Immediate type, urticarial reactions were seen in 13% to 27% of positive APT reactions. The κ-tests showed statistically significant agreement between the different pairs of APT, serum specific IgE and SPT, although the strength of agreement varied between fair and substantial.

Conclusion

We found a substantial number of clear-cut positive APT reactions, with a relatively high percentage of urticarial reactions. We would like to prompt increased interest in the immediate type, urticarial reactions in the APT, especially in children.

Introduction

Sensitization to aeroallergens, commonly associated with direct type, IgE mediated allergy, is a common finding in both pediatric and adults patients with atopic dermatitis (AD). The exact role of this sensitization in the pathogenesis of AD remains controversial. There does seem to be a subgroup of patients with AD where contact with aeroallergens, such as house dust mite or grass pollen, is capable of worsening eczematous skin lesions.[1] Adequate avoidance measures may be helpful in controlling AD in these patients, although results from clinical trails are contra dictionary.[2-4]

Additional evidence for a possible role of aeroallergens in the pathogenesis of AD is found in the fact that epicutaneous application of these allergens can elicit delayed type, eczematous skin reactions in patients with AD.[5,6] This so-called Atopy Patch Test (APT) was first described in detail in 1982 and has been the focus of increased research interest over the last 10-15 years.[7] The APT is currently widely accepted as an in vivo model of AD.[8] However, differences in methodology and the lack of a golden standard for the presence of a relevant sensitization to aeroallergens in AD are two major obstacles in the development of the APT as an addition to our allergologic work-up in patients with AD.[7,9]

Most of the current clinical data on the APT with aeroallergens is based on adult patient populations and pediatric data is scarce. We initiated a prospective clinical study in children with AD up to 3 years age, to evaluate the presence of positive APT reactions and their correlation with elevated levels of serum specific IgE and/or the presence of positive Skin Prick Test (SPT) reactions.

Materials and Methods

The study was performed on the pediatric dermatology out-patient clinic of the Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands. Children below the age of 3 years with AD and an indication for an allergologic work-up, were eligible for inclusion. AD was defined by the criteria of Williams et al.[10] Indications for an allergologic work-up consisted of refractory skin disease or suspected allergy to aero- or food allergens due to reported reactions after exposure or pre-existing diets. The inclusion period lasted 2 years and 10 months. All patients were subjected to a careful history of possible allergic symptoms, combined with measurement of serum specific IgE and the APT. Additional Skin Prick Test (SPT) were only performed in children older than 1 year of age. Investigated allergens included dog dander, cat dander and house dust mite. Allergens for the SPT and APT were obtained from ALK-Abello and consisted of aqueous solutions with an allergen concentration of 10.000 PNU. Severity of AD at the time of the skin tests was measured using the objective SCORAD.[11]

Atopy Patch Test

APT were performed on the unabraded skin of the back using normal (8 mm) Finn-chambers on scanpor®. The buffer solution was tested as a negative control. After 20-30 minutes the test areas were examined to exclude urticarial weal and flare reactions, in which case the skin test would be removed. Subsequently the test chambers were covered with fixomull®, to prevent them from shifting. After 48 hours the test chambers were removed. Evaluation of the skin tests took place after 48 and 72 hours, using the guidelines described by the European Taskforce on Atopic Dermatitis (ETFAD).[12] Clear-cut reactions of 2+ or more were regarded as positive. Urticarial reactions were also included as positive, immediate type APT reactions.

Specific IgE

Blood was drawn from each patient. Allergen-specific IgE was measured in serum with the CAP system (Pharmacia, Woerden, The Netherlands) according to the manufacturer's instructions. Only levels of 0,70 U/l, or above were regarded as positive.

Skin Prick Test

A drop of the solution was applied on the volar surface of forearm, after which a lancet was used to penetrate the skin through the drop. Histamine was tested as a positive control. The results were evaluated by measuring the mean diameter of the wheal reaction after 15 and 30 minutes. A positive reaction consisted of a wheal, which had a mean diameter of at least 3 mm and was at least half the diameter of the positive control.

Ethical aspects and statistical analysis

The study was approved by the Medical Ethics Committee of the Erasmus MC, Rotterdam, The Netherlands. The parents of all patients signed informed consent. The statistical analysis was performed using SPSS version 11.0. Statistical analysis was performed in patients with complete data necessary for the calculations. Because of missing test results in some patients the n-value varies between statistical calculations. There was no suspicion that missing data occurred selectively and we could not detect a bias in patient characteristics such as age, sex or severity of AD. The kappa (κ) statistic was used for quantifying and testing agreement between the various test scores. The strength of agreement is interpreted as described by Landis and Koch.[13]

Results

One hundred and forty eight children were eligible for inclusion. We experienced 13 dropouts due to active skin disease on the test areas (n=8), very strong positive dermography (n=1), multiple positive APT reactions, including the negative control (angry back, n=3) and 1 child who developed fever based on an airway infection during the test week. This left 135 children included, with an age distribution from 5 to 35 months and a mean age of 20 months with a standard deviation of 9 months. The mean objective SCORAD score was 13.6 with a standard deviation of 8.3. There were 51 (38%) girls and 84 (62,2%) boys. SPT were only performed in children above the age of 1 year (n=102/135).

	APT positive		APT negative	
	Freq.	**Perc.**	**Freq.**	**Perc.**
Dog (n=120)	15	12.5%	105	87.5%
HDM (n=122)	30	25%	92	75%
Cat (n=124)	27	22%	97	78%

Table 1
Frequency and percentages of positive and negative atopy patch test (APT) results. Results are shown for the 3 different aeroallergens: dog dander, house dust mite (HDM) and cat dander.

Table 1 lists the number and percentages of positive and negative APT results for the 3 different aero-allergens. The majority of positive APT reactions consisted of classical delayed type eczematous reactions. However, immediate type, urticarial reactions were seen in 4/15 (27%) of the tests with dog dander, 4/30 (13%) of the tests with HDM and 6/27 (22%) of the tests with cat dander. All patients with immediate type, urticarial reactions showed elevated levels of specific IgE and/or a positive SPT reaction.

Number of allergens	**APT positive** (n=116)	**IgE positive** (n=123)	**SPT positive** (n=104)
0	70 (60.3%)	72 (58.5%)	64 (61.5%)
1	28 (24.1%)	22 (17.9%)	17 (16.3%)
2	14 (12.1%)	23 (18.7%)	18 (17.3%)
3	4 (3.4%)	6 (4.9%)	5 (4.8%)

Table 2
Frequency and percentages of patients with positive reactions to 0,1,2 or 3 of the aeroallergens in respectively the atopy patch test (APT), serum specific IgE measurement or skin prick test (SPT).

Sensitization to more than one allergen was found in the APT as well as in measurement of specific IgE and the SPT. Details are listed in table 2. All patients with more than 1 positive APT reaction showed consistency in the type of APT reaction. They either had immediate type urticarial reactions or delayed type eczematous reactions. We did not find any patients with both reaction types.

	N	Strength of agreement	κ-value	p-value
APT vs. IgE				
Dog	115	Fair	0.27	0.005
HDM	119	Fair	0.38	< 0.0005
Cat	120	Fair	0.38	< 0.0005
APT vs. SPT				
Dog	93	Moderate	0.53	< 0.0005
HDM	95	Fair	0.31	0.003
Cat	97	Fair	0.39	< 0.0005
SPT vs. IgE				
Dog	98	Moderate	0.5	< 0.0005
HDM	101	Substantial	0.77	< 0.0005
Cat	99	Moderate	0.57	< 0.0005

Table 3
Agreement between the atopy patch test (APT), serum specific IgE measurement and skin prick test (SPT) as was calculated using the kappa-test. Results are shown for the 3 different aeroallergens dog dander, house dust mite (HDM) and cat dander.

The agreement between different tests is detailed in table 3. The κ-tests showed statistically significant agreement between all three pairs of tests, although the strength of agreement varied between fair and substantial. We did not find any statistically significant impact on the data described above by either sex or age.

Discussion

Our study was performed using dog dander, cat dander and HDM as common indoor aeroallergens. We found clear-cut positive APT reactions in respectively 12.5%, 22% and 25% of our patient population. Positive APT reactions to HDM were most frequent, which is in concordance with earlier literature on adult patients. [6,9] The frequency of positive APT to HDM seem to be higher in adult patients, with reported frequencies around 40%.[6,9] In contrast we seem be find more positive APT to cat dander in our patient population compared to the reported frequencies of 10% to 15% in adult patients. [6,9]

In our patient population there was a statistically significant but only fair agreement between the APT and the presence of specific IgE or the SPT. Positive delayed type APT reactions were also found in patients without specific IgE or positive SPT, suggesting that positive APT reactions may be facilitated by specific IgE but are not dependant on its presence. This is in concordance with the current understanding of the pathogenesis of the

APT.[7,8] Unlike a recent publication from Mohrenschlager et al, we did not find any differences in APT, serum specific IgE and SPT reactivity between boys and girls.[14] There were also no detectable differences between these parameters when we divided our patients into different age-groups. We could not find a correlation between the presence of positive APT reactions and the objective SCORAD at the time of the skin tests (data not shown). As there is no gold standard for the diagnosis of a relevant allergy to aeroallergens in patients with AD, we did not attempt any conclusions with regard to the clinical relevance of the positive APT reactions.

We found a relatively high number (13-27%) of immediate type, urticarial APT reactions in our patient population. These urticarial reactions were only found in patients with elevated serum levels of specific IgE and/or positive SPT's against the allergen tested. Several test sites with urticarial reactions showed clear-cut delayed type, eczematous reactions after 48 and 72 hours, even though the skin test itself was removed after 20-30 minutes [personal observation]. Our relatively young patient population may be largely responsible for the relatively high percentage of urticarial reactions.[15] One hypothesis could be that allergens are able to penetrate the epidermis of young children with AD more readily than in adults with AD. However, we believe there might also be an underreporting of immediate type, urticarial APT reactions in the current literature.

Unfortunately, as is often the case in studies on the APT, our study methodology is not completely comparable to the above cited adult studies. Next to the age difference of the patient populations, the most obvious difference is in the allergen preparations that were used. From a practical point of view we chose to use the same aqueous allergen solutions for the SPT as well as the APT, whereas petrolatum based allergen preparations were used in most recent adult studies. Based on current knowledge these petrolatum based preparations are preferable for further standardization of the APT.[8] Despite this reservation we believe the data described above adds valuable information to our currently knowledge of the APT with aeroallergens in children.

In conclusion we found a substantial number of clear-cut positive APT reactions to three common aeroallergens, with a relatively high percentage of urticarial reactions, in our patient population of young children with AD. Although the APT seems promising as a diagnostic and possibly even prognostic skin test, its clinical value still appears limited at the moment.[8,16] Further studies aimed at standardization, reproducibility and clinical validation in children as well as adults are needed before the APT with aeroallergens can be used in routine daily clinical practice.[8] For future use we would like to prompt increased interest in the immediate type urticarial reactions in the APT, especially in children.

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Chapter 4

Matrix metolloproteinase-9: an objective marker for the severity of atopic dermatitis?

Elevated levels of plasma MMP-9 in patients with atopic dermatitis: a pilot study

A.C.A. Devillers, A.W. van Toorenenbergen, G.J. Klein Heerenbrink, P.G.H.Mulder, A.P. Oranje

Clin Exp Dermatol 2007; 32(3):311-313

Elevated levels of plasma MMP-9 in patients with atopic dermatitis: a pilot study

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Matrix Metalloproteinase (MMP)-9 has been shown to play a role in the infiltration of inflammatory cells in different tissues. It is thus part of the pathogenesis of many inflammatory diseases, including asthma and allergic rhinitis/conjunctivitis. We compared plasma MMP-9 levels of 20 patients with atopic dermatitis (AD) to that of 17 control subjects. Additional outcome parameters consisted of the modified-objective SCORAD and the Three Item Severity score (TIS) in patients, peripheral blood leukocytes and eosinophils in both groups. Plasma MMP-9 levels were found to be significantly higher in patients compared to controls, supporting a role of MMP-9 in the pathogenesis of AD.

Introduction

Matrix metalloproteinases (MMPs) form a group of zinc-dependent enzymes, which are capable of hydrolysing protein structures in the extra-cellular matrix (ECM) of tissues, thus playing a role in invasive tumour growth, tissue remodelling and infiltration of inflammatory cells in tissues.[1] Through cleavage they also play a role in shedding of cell membrane associated proteins and activation of pro-enzymes, thus being integrated in the inter-cellular signalling pathways.[1] MMP activity is regulated by endogenous tissue inhibitors of metalloproteinases (TIMPs).

Various studies suggest that MMP-9 plays a role in the formation of the allergic inflammation as seen in the lungs and nasal mucosa of patients with asthma and allergic rhinitis.[2,3] In vivo studies have also reported an increased expression of MMP-9 in human skin samples of positive patch tests as well as positive atopy patch tests.[4,5] Based on this we hypothesised that MMP-9 could be important in the pathogenesis of atopic dermatitis (AD).

Report

The study was approved by the Ethical Committee of the Erasmus MC and all participants signed informed consent. Twenty patients with AD (male: female =11:9) and 17 healthy, non-atopic controls (male: female =4:13) were included. AD was defined using the criteria as described by Williams et al.[6] No systemic or phototherapy was allowed for four weeks prior to inclusion. Topical treatment consisted of emollients and once daily topical corticosteroids if necessary. The severity of skin lesions was assessed using the modified-objective SCORAD and Three Item Severity score (TIS).[7,8] MMP-9 was determined in plasma, collected from Li-heparin tubes. Plasma samples were stored at -20 degree Celsius. Human MMP-9 was determined with an Elisa obtained from R&D systems (Abingdon, United Kingdom), according to the manufacturers' instructions. This Elisa (product code DMP900) measures total MMP-9, composed of active as well as pro-MMP-9. Allergen-specific IgE against house dust mite, grass and cat dander was measured in serum with the CAP system (Pharmacia, Woerden, The Netherlands) according to the manufacturer's instructions. The absolute amounts of leukocytes and eosinophils were determined with the Sysmex XE-2100 electronic cell counter (Goffin Meyvis, Etten-Leur, The Netherlands). The statistical analysis was performed using SPSS 11.0. Because of the non-symmetric distributions of the variables involved, we used nonparametric statistical tests: the Mann-Whitney test for comparison of the two groups and the Spearman rank correlation test for the relationships between the variables.

Twelve of 20 patients had a history of asthma. Only 2 of these 12 patients had active disease, controlled with corticosteroids via inhalation. None of 16 patients with a history of allergic rhinitis/conjunctivitis had active disease or used any medication. Seventeen patients showed elevated levels of specific IgE (> 0.70 IE/ml) against one or more of the aero-allergens tested. The mean modified objective SCORAD in the patient group was 27.1 (13-46). Non-parametric analysis, using the Mann-Whitney test, showed significantly higher levels of plasma MMP-9 ($p<0.0005$) in the patient group as compared to the control group (table 1).

	Patients			Controls			P (2-sided)
	Median	Minimum	Maximum	Median	Minimum	Maximum	
MMP9 (ng/ml) N=20 vs. N=17	264.78	64	917	31.27	11	131	<0.0005
Leucocytes (10^9/l) N=20 vs. N=17	6.05	3.40	11.30	6.57	5.10	9.38	0.156
Eosinophils (10^9/l) N=17 vs. N=17	0.39	0.07	1.53	0.09	0.04	0.34	<0.0005

Table 1

Non-parametric analysis, using the Mann-Whitney test, of plasma MMP9 values, leukocyte counts and eosinophilic granulocyte counts in peripheral blood of patients with AD versus control subjects.

The absolute amounts of leukocytes were not significantly different between both groups. Using Spearman's rank correlation test there was a significant correlation between plasma MMP-9 and the absolute amount of leukocytes in patients ($r=0.48$, $p=0.033$), but not in controls ($r=0.076$, $p=0.772$) (fig. 1). Although there were a significantly higher number of eosinophils present in the peripheral blood of patients compared to controls, there was no significant correlation with plasma MMP-9 levels in either group (respectively $r=0.052$, $p=0.844$ and $r=-0.137$, $p=0.601$). No statistically significant correlation could be found between plasma MMP-9 and the modified-objective SCORAD ($r=0.005$, $p=0.985$) or the TIS ($r=-0.28$, $p=0.912$).

This study shows significantly increased levels of MMP-9 in plasma of patients with AD as compared to healthy controls, suggesting a role for MMP-9 in the pathogenesis of AD. A possible explanation for the correlation between the absolute amount of leukocytes in peripheral blood and plasma MMP-9 in our patient group, might be that in active AD the number of peripheral blood leukocytes reflects the intensity of skin inflammation and thus the level of plasma MMP-9. Peripheral blood MMP-9 levels in asthma and chronic urticaria have been shown to correlate with disease severity.[9] However, in our patients we could not find a significant correlation between plasma MMP-9 levels and the modified-objective SCORAD or TIS, as markers of disease severity.

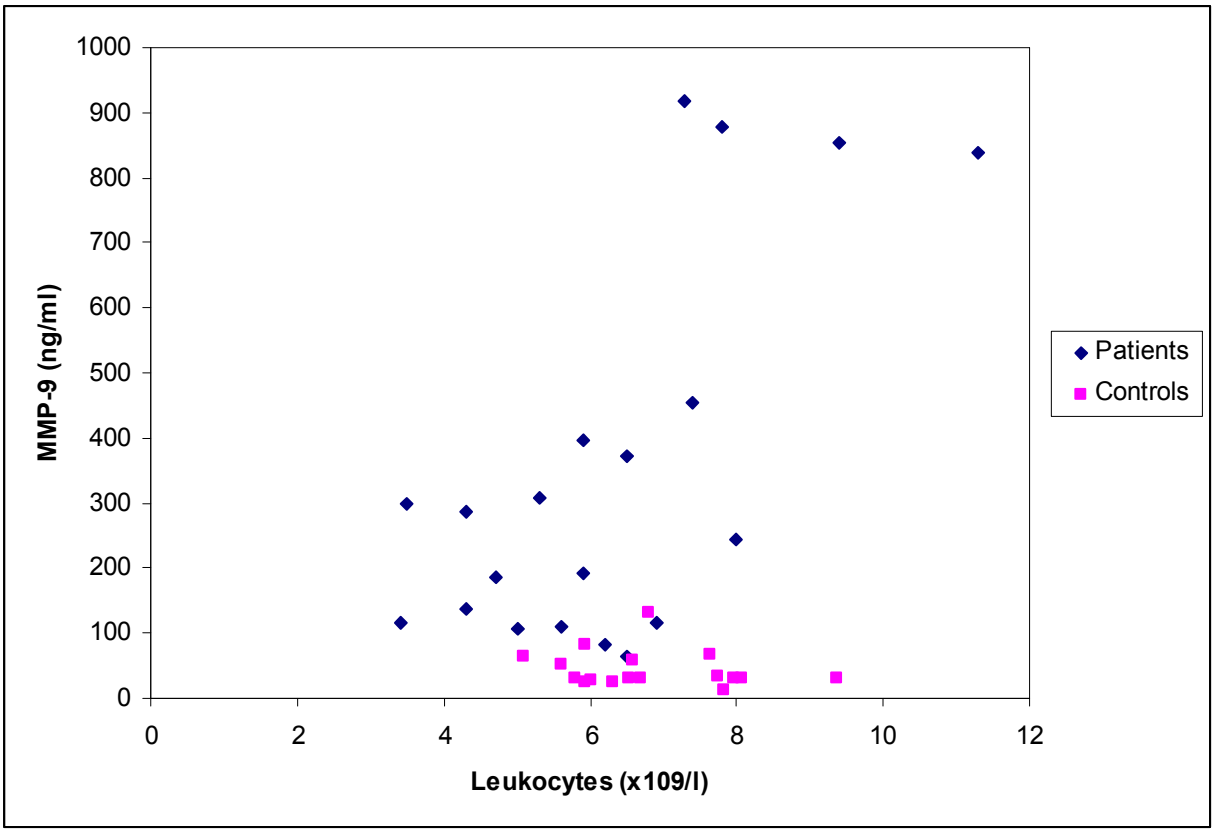

Fig 1
Plasma MMP-9 versus absolute amount of leukocytes in patients and healthy control subjects. Non-parametric analysis, using Spearman's rank correlation test, showed a significant correlation in the patient group (r=0,48; p=0,033), while no significant correlation was observed in the control group.

Although our patients and the control group are not perfectly matched with regard to age and especially gender, we believe this does not affect our findings. Both parameters were previously found to have no effect on circulating MMP-9 in healthy controls.[10] In addition we also found plasma MMP-9 values in our control group, which are comparable to values found by Kessel et al, who used a very similar methodology.[9] Only two of our patients had active airway disease, adequately controlled with corticosteroids via inhalation. For this pilot study we did not exclude them in our results, although a possible influence of the airway disease and/or the medication cannot be excluded. Further, larger studies are needed to evaluate plasma MMP-9 levels in AD, including stratification for concomitant asthma and allergic rhinitis.

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Chapter 5

"wet-wrap" dressings as a treatment modality in atopic dermatitis

Treatment of refractory atopic dermatitis using "wet-wrap" dressings and diluted corticosteroids: results of standardized treatment in both children and adults.
A.C.A. Devillers, F.B. de Waard-van der Spek, P.G.H. Mulder, A.P. Oranje.
Dermatology 2002; 204:50-55

Efficacy and safety of "wet-wrap" dressings as an intervention treatment in children with severe and/or refractory atopic dermatitis: a critical review of the literature
A.C.A. Devillers, A.P. Oranje.
Br J Dermatol 2006; 154:579-585

Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert's opinion and review of the literature
A.P. Oranje, A.C.A. Devillers, B. Kunz, S.L. Jones, D. Van Gysel, F.B. de Waard-van der Spek, R. Grimalt, A. Torello, J. Stevens, J. Harper
J Eur Acad Dermatol Venereol 2006; 20:1277-1286

"Wet-wrap" treatment in children with atopic dermatitis: a practical guideline
A.C.A. Devillers, A.P. Oranje
Pediatr Dermatol (accepted for publication)

Treatment of refractory atopic dermatitis using "wet-wrap" dressings and diluted corticosteroids: results of standardized treatment in both children and adults

A.C.A. Devillers, F.B. de Waard-van der Spek, P.G.H. Mulder, A.P. Oranje

Dermatology 2002; 204:50-55

Background

"Wet-wrap" dressings with diluted corticosteroids form an alternative treatment in patients with refractory atopic dermatitis

Objective

To evaluate a standardized treatment, using "wet-wrap" dressings with diluted corticosteroids, in patients with refractory atopic dermatitis.

Methods

Results of treatment, complications and possible side effects were evaluated in 14 children and 12 adults.

Results

Skin lesions improved dramatically during 1 week of in-patient treatment. A significant decrease in early-morning serum cortisol levels was measured. Levels below the normal range were only observed after 1 week in 2 adults and on day 4 in 3 children. Suppression of the hypothalamic-pituitary-adrenal cortex-axis in 1 adult and a new exacerbation of atopic dermatitis in 2 children and 3 adults complicated long-term treatment at home. Additional complications included folliculitis, a Pseudomonas aeroginosa infection, secondary bacterial infection and refractory skin lesions between bandages.

Conclusion

"Wet-wrap" dressings and diluted corticosteroids form an effective treatment in patients with refractory atopic dermatitis.

Introduction

Emollient and topical corticosteroids are the mainstay in the treatment of atopic dermatitis. Unfortunately there are patients who are unresponsive to conventional therapy. Current intervention treatments for patients with refractory atopic dermatitis (AD) consist of cyclosporine A, systemic corticosteroids, phototherapy and photo-chemotherapy. More experimental treatments, such as recombinant interferon γ and high doses of immunoglobulines intravenously, are also available. Each one of these treatments has its own drawbacks and side effects, limiting its use in daily practice. "Wet-wrap" dressings and diluted corticosteroids form a recently developed alternative for patients with severe and refractory AD. Long-term treatment at home seems feasible. We studied the results of a standardized treatment, using "wet-wrap" dressings and corticosteroids in patients with refractory AD.

Patients and Methods

Adults and children with refractory AD, as defined by Hanifin and Rajka and Sampson and Williams et al., respectively, who visited our (pediatric) dermatology out-patient clinic between March 1999 and March 2000, were eligible for treatment according to a standardized protocol.

In-patient treatment

Treatment was started on day 1. Details are listed in table 1. In short, patients bathed for 5-10 minutes in lukewarm water, followed by application of diluted fluticasone propionate 0.05% (FP) cream on the entire body. Then a wet layer of tubular bandage was applied, followed by a second dry layer. The first layer was re-wetted every 2-3 hours. On the facial skin a 5% dilution of FP cream was used. A side-to-side treatment was started on the body, consisting of a 10% and a 25% dilution in adults and a 5% versus a 10% dilution in children. The entire procedure was repeated once daily, during a period of 1 week.

Follow-up

After patients were discharged from the hospital, the treatment was continued at home for four consecutive days. Diluted FP cream was now only used on clinically involved skin, applying emollient on uninvolved skin. In the next three days of the week, only emollient was applied to the skin. Depending on the severity of the symptoms, the number of days with the "wet-wrap" treatment was adjusted, with a maximum of 5 days a week.

1.	Chose the appropriate width of the tubular bandages and cut these to size to fit the arms, legs and trunk. Cut a facial mask if necessary.
2.	Apply the appropriate dilution of fluticasone propionate 0,05% (FP) cream on the skin
3.	Wet the individual pieces of tubular bandage in lukewarm water.
4.	Apply the first layer of wet tubular bandage. Connect the arm and leg pieces to the trunk. Use the facial mask if necessary.
5.	Apply the second layer of dry tubular bandage. Again connect the arm and leg pieces to the trunk. Use the facial mask if necessary.
6.	Re-wet the bandages every 2 to 3 hours.
7.	Repeat the above mentioned procedures daily.
8.	After one week of treatment the diluted FP cream is only applied on the clinically involved skin for 3-5 consecutive days of the week. Emollient is applied on the uninvolved skin. Patients can perform the treatment at home.

Table 1
Methodology of the "wet-wrap" treatment using diluted fluticasone propionate 0,05% cream. (According to Oranje, based on the method as described by Goodyear et al.)

Safety

Early-morning cortisol levels were measured before and after 1 week of treatment to assess the systemic load of the topical corticosteroids. Blood samples were drawn in adults and children at 8:00 and 6:00 a.m., respectively. Reference values show a lower limit of 200 nmol/l. In children, an additional value was measured on day 4. During follow-up, the measurements of early-morning cortisol were repeated according to protocol. Weight and height of the children were recorded.

Disease severity

Severity of AD was evaluated using the objective SCORAD score. This scoring system combines the extent of the skin lesions and the intensity of six clinical features of AD. The objective SCORAD was performed on day 0 as well as on day 7. During follow-up the score was repeated at regular intervals.

Statistic analyses

The statistic analyses was performed using SPSS 9.0. The change in objective SCORAD was analyzed using a paired T-test. The data of the early-morning cortisol levels were analyzed using the Wilcoxon's signed rank test . Significance was defined as $p<0.05\%$ (2-sided)

Results

Fourteen children and 12 adults with refractory AD were treated according to protocol. The group of children included 8 girls and 6 boys, aged between 6 months and 10 years and 1 month (average 3 years and 1 month). The adults included 7 women and 5 men, aged between 18 years and 61 years and 3 months (average 29 years and 11 months). The average follow-up lasted 17 weeks (11-41). Two adults were lost to follow-up after 1 and 8, weeks respectively.

Hospitalization

Thirteen children and 2 adults were treated using the "wet-wrap" dressings including a facial mask. The remaining patients did not use a facial mask at their own request or due to absence of facial skin lesions. Three children and 10 adults used additional mild to moderate topical corticosteroids in order to treat facial or scalp lesions. Because of bronchitis two adults used FP 125 μg twice a day via an inhaler. For the same reason, one adult used 500 μg FP twice a day via an inhaler, combined with prednisone 5 mg once a day orally. Prednisone was discontinued during his hospitalization.

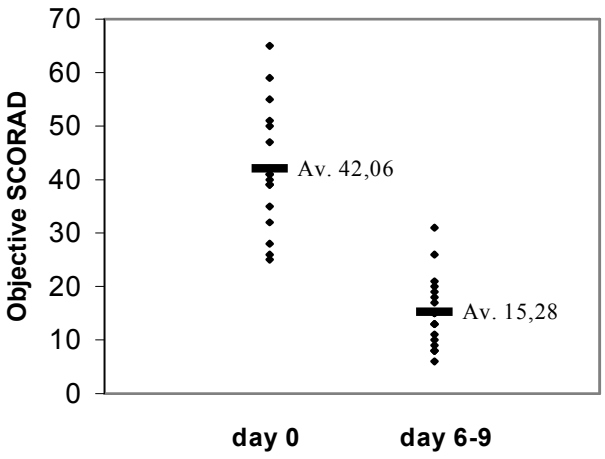

Figure 1
Disease severity, before and after 1 week of treatment, as reflected in the (mean) objective SCORAD (n=18).

A marked improvement of skin lesions was noted in all patients. Objective SCORAD scores, before and after treatment, were available in 18 cases (figure 1). Using a paired T-test, a significant decrease of 26.78 points in the objective SCORAD was observed after 6-9 days (table 2). Individual analysis of the children and adults showed a decrease of 25.43 and 27.62 points, respectively. In 1 child and 4 adults a difference was observed at day 4/5 in

favor of the less diluted and thus more potent concentration of FP cream (1:9 and 1:3, respectively). In the other 21 patients no differences between both sides were observed.

	SCORAD (day 0)	SCORAD (day 6-9)	Decrease in SCORAD	95% CI		p-value (2-sided)
				Lower value	Upper value	
Total (n=18)	**42.06**	**15.28**	**26.78**	**21.90**	**31.65**	**<0.0005**
Children (n=11)	**39.09**	**11.45**	**27.64**	**20.87**	**34.40**	**< 0.0005**
Adults (n=7)	**46.71**	**21.28**	**25.43**	**16.18**	**34.67**	**< 0.0005**

Table 2.
Improvement of disease severity during treatment, reflected in a significant decrease in the mean objective SCORAD between day 0 and day 6-9. Data are given for the group as a whole and for children and adults separately. The analysis was performed using a paired T-test.

Planned early-morning cortisol levels before and after treatment were available for 24 patients (figure 2 and 3). Using Wilcoxon's signed rank test, a significant decrease in cortisol levels was observed after treatment (table 3). On individual analysis of both children and adults, this decrease was still significant. No children and only 2 adults showed cortisol levels below 200 nmol/ml at the end of treatment. Both adults used additional topical corticosteroids on face and scalp. One patient had been treated with the less diluted and more potent concentration of FP cream (1:3) after day 5 and the other one used FP via an inhaler. The patient using prednisone orally, had cortisol levels below 200 nmol/ml both before and after treatment. No significant decrease was observed between the cortisol levels on day 1 and day 4. However, 3 children showed a temporary drop below200 nmol/ml, which had normalized at the end of the week, despite continuation of the treatment One of these children had used mild topical corticosteroids on the scalp. Further complications were limited to a mild localized folliculitis.

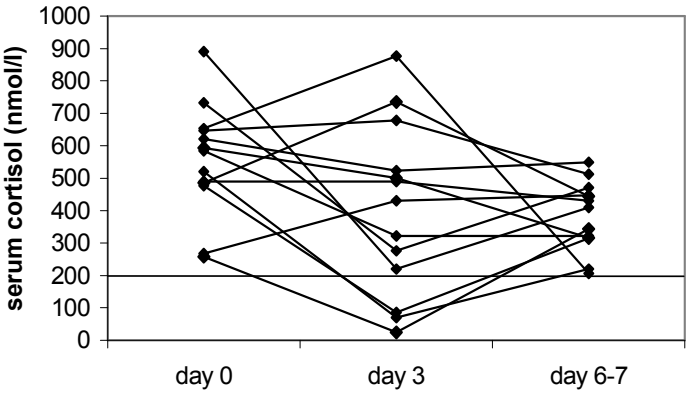

Figure 2.
Course of early-morning serum cortisol levels during hospitalization in 13 children.

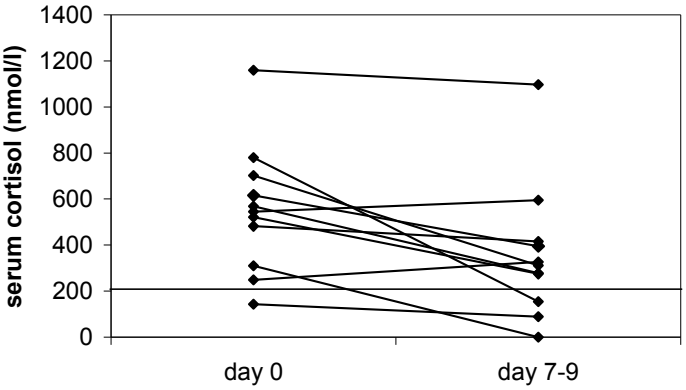

Figure 3.
Course of early-morning serum cortisol levels during hospitalization in 11 adults.

	Cortisol levels day 0 (nmol/l)			Cortisol levels day 6-9 (nmol/l)			Z	P (2-sided)
	Min.	Max.	Median	Min.	Max.	Median		
Total (n=24)	**144**	**1159**	**557**	**<0.27**	**1096**	**335**	**-3.40**	**<0.001**
Children (n=13)	**258**	**890**	**585**	**206**	**549**	**410**	**-2.41**	**<0.016**
Adults (n=11)	**144**	**1159**	**545**	**<0.27**	**1096**	**312**	**-2.40**	**<0.016**

Table 3
Early-morning serum cortisol levels are listed for the group as a whole and for children and adults separately. A significant decrease during one week of treatment was noted in all three groups. The analysis was performed using Wilcoxon's signed rank test.

Follow-up.

Exacerbations of AD, cortisol levels below 200 nmol/ml and further complications are summarized in table 4. Exacerbations of AD occurred in 2 children and 3 adults. Interventions consisted of cyclosporine A (1), renewed hospitalization for treatment with tar ointment (3) and prednisone orally in 1 child with simultaneous respiratory distress. After the intervention, 2 patients continued and 3 patients discontinued the "wet-wrap" treatment at home.

Temporary cortisol levels below 200 nmol/ml were observed in 2 children and 1 adult man, who used FP via an inhaler, combined with frequent episodes of prednisone orally. The 2 children did not use any additional corticosteroids. Their height and weight remained unaffected. One adult, who also used FP via an inhaler, developed a prolonged suppression of his hypothalamus-pituitary-adrenal cortex (HPA) axis, in combination with several striae on his abdomen.

Complications during long-term treatment at home	Number (n=24)
Severity of disease	
- Exacerbation AD	5
Systemic bioactivity	
- Temporary cortisol levels <200 nmol/l	3
- Prolonged suppression HPA-axis	1
Further complications	
- Infectious	9
- Refractory skin lesions on hips	1
- Striae on abdomen	1
- Deviated growth	1

Table 4
The complications occurring during long-term treatment at home, divided in three categories. Two patients were lost to follow-up after 1 and 8 weeks, respectively. HPA-axis = Hypothalamus-Pituitary-Adrenal cortex-axis

Further complications consisted of localized folliculitis (4), secondary impetigo (2), a localized Pseudomonas aeroginosa infection, cellulitis of the left cheek in a patient without a facial mask and a purulent conjunctivitis in a patient with a facial mask. The last patient reported frequent episodes of conjunctivitis in the past. One child showed refractory skin lesions on his hips and buttocks and one child showed a deviation in his growth, without any abnormal cortisol levels. Retrospectively the growth deviation had started before the start of the "wet-wrap" treatment and was the result of a low food intake. His eating habits improved, with help from our dietician. Subsequently, he caught up with his estimated growth curve, despite continuation of treatment.

Discussion

In 1991, Goodyear et. al. described a highly effective "wet-wrap" treatment with diluted topical corticosteroids in children with severe erythrodermic atopic dermatitis.[10] In our department we established a modified protocol using a dilution of FP cream (table 1).[11,12] FP cream is a potent corticosteroid with an improved benefit/risk ratio.[18,19] The use of this protocol in the treatment of patients with refractory AD has been shown to be very effective.[11,12] The greatest improvement in AD occurs in the first week of treatment.[12] The use of a less potent dilution of FP cream shows a comparable high efficacy, with a lower risk of systemic bioactivity.[12] The mode of action of the "wet-wrap" treatment is a combination of reduction of pruritis and inflammation by cooling of the skin, increased penetration of topical corticosteroids by creating an occlusive and moist environment and protection of the skin against scratching.

The current retrospective study confirms the efficacy and safety of this standardized treatment in patients with refractory AD. Thirteen children and 8 adults continued treatment with the less potent dilution of FP after day 4-5 (1:19 and 1:9 respectively). Despite a significant decrease in early-morning cortisol levels in both groups, only 2 adults developed a cortisol level below 200 nmol/l during hospitalization. One of them developed a prolonged suppression of his HPA-axis during follow-up. The low cortisol levels may be explained by the use of more potent dilutions of FP cream after day 4-5, the use of additional topical or inhaled corticosteroids and an increased individual sensitivity to corticosteroids. The temporarily decreased cortisol levels below 200 nmol/l in 3 children halfway treatment were remarkable. A possible explanation is provided by a repair of the barrier function of the skin during treatment, causing a decreased penetration at the end of the treatment.

The use of early-morning serum cortisol levels as a parameter of systemic side effects, is an easy but rather insensitive method due to a large inter- and intra-individual variability.[20] An improved sensitivity and specificity might be achieved using early-morning cortisol/creatinine ratios in urine or cortisol levels in saliva. [21,22] These methods are also less invasive, which is an additional advantage, especially in children.

Folliculitis is a well-known side effect of the "wet-wrap" treatment, probably due to its occlusive effect.[12] Use of diluted corticosteroids may suppress the process, however, also aggravate it in some cases. The localized Pseudomonas aeroginosa infection was remarkable. Possibly, the moist environment under the bandages was involved. The water sprayer, which was used to re-wet the bandages, may have acted as a source of infection, due to insufficient cleaning. Patients with AD are at risk for secondary bacterial infections due to a decreased skin barrier among other things. It is possible that the "wet-wrap" treatment with diluted corticosteroids increases this risk, but to what extent is unknown. Obviously the "wet-wrap" treatment should be stopped during episodes of secondary bacterial infections. Refractory skin lesions on the connection between two bandages are a known problem. A connection between the treatment and the occurrence of cellulitis, purulent conjunctivitis and the growth deviation is very unlikely.

Conclusion

The "wet-wrap" treatment with diluted corticosteroids, as described above, is a very effective treatment in patients with severe and refractory AD. The most important side effect consists of a (temporary) suppression of the HPA-axis in a minority of the patients. The use of a less potent dilution of FP cream diminishes this risk, while maintaining a good

efficacy. In children a 1:19 dilution of FP cream is advised. Long-term treatment at home is feasible when patients (and parents) are motivated and provided with adequate instruction and guidance. A day-care center, with dermatologically qualified nurses, provides an excellent setting for the follow-up of these patients.

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Efficacy and safety of "wet-wrap" dressings as an intervention treatment in children with severe and/or refractory Atopic Dermatitis: a critical review of the literature

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Background

During the last 2 decades wet-wrap treatment (WWT) has been advocated as a relatively safe and effective treatment modality in children with severe and/or refractory atopic dermatitis (AD). Unfortunately, there are still many unsolved issues concerning the use of wet-wrap dressings in patients with AD.

Objectives

To make an inventory of the different methodologies and to evaluate the currently available evidence for the use of WWT as an intervention treatment in children with severe and/or refractory AD

Methods

We performed a search of the literature via the online PubMed database. Reference lists from relevant articles were scanned for additional publications. Publications describing a treatment modality for children with severe and/or refractory AD, which included the application of wet dressings, were collected and evaluated using the guidelines of the NHS Centre for Reviews and Dissemination, University of York (CRD).

Results

Twenty-four publications were included for evaluation. Eleven of the publications detailed original clinical studies (study design level 2-4), while 13 revealed expert's opinions (study design level 5). Evidence levels did not exceed level 4

Conclusions

Large prospective studies evaluating the efficacy and safety profile of WWT are lacking. We were able to formulate the following conclusions with a grade C of recommendation. (i) WWT using cream or ointment and a double layer of cotton bandages with a moist first layer and a dry second layer, is an efficacious short-term intervention treatment in children with severe and/or refractory AD. (ii) The use of wet-wrap dressings with diluted topical corticosteroids is a more efficacious short-term intervention treatment in children with severe and/or refractory AD than wet-wrap dressings with emollients only. (iii) The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD, with temporary systemic bioactivity of the corticosteroids as the only reported serious side effect. (iv) Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution of the product can reduce the risk of systemic bioactivity.

Introduction

The treatment of children with atopic dermatitis (AD) can be challenging for medical professionals as well as patients and their parents. Conventional treatment, consisting of emollients and topical corticosteroids, is not always sufficient, even when combined with appropriate information and guidance. Recently, topical calcineurin inhibitors have been introduced as an alternative treatment option in children older than 2 years. Although they are a welcome addition to our therapeutic arsenal, they are not more effective than potent topical corticosteroids.[1]

Known intervention treatments for severe and/or refractory AD include systemic corticosteroids, cyclosporine A, azathioprine and photo(chemo)therapy.[2,3,4,5] All of these interventions have their potential side effects and (relative) contraindications, especially in children. During the last two decades wet-wrap treatment (WWT) has been advocated as a relatively safe and effective treatment modality in children with severe and/or refractory AD. Despite several publications from different research groups, there are still many unsolved issues concerning the use of wet-wrap dressings in the treatment of AD. We performed a review of the literature in order to make an inventory of the different methodologies and to evaluate the currently available evidence for the use of WWT as an intervention treatment in children with severe and/or refractory AD.

Review questions

The following review questions were drawn up based on a population of children with severe and/or refractory AD. WWT was defined as a treatment modality using a double layer of tubular bandages or gauze, with a moist first layer and a dry second layer.

1. In which ways does the methodology of the treatment with wet-wrap dressings differ between the publications?
2. Is the use of wet-wrap dressings an efficacious intervention treatment modality?
3. Is the use of wet-wrap dressings with (diluted) topical corticosteroids more efficacious than the use of wet-wrap dressings with emollients or emollients in combination with antiseptics?
4. Is the use of wet-wrap dressings with (diluted) topical corticosteroids a safe intervention treatment modality?

Methods

We performed a search of the literature via the online PubMed database. Different search strings were entered using the keywords "wet-wrap" and "wet dressings" alone or in combination with "atopic dermatitis" and "atopic eczema". Reference lists from relevant articles were scanned for additional publications.

Publications describing a treatment modality for children with severe and/or refractory atopic dermatitis, which included the application of wet dressings, were collected. The publications were then divided according to primary study design hierarchy as described in the guidelines of the Centre for Reviews and Dissemination, University of York (CRD, level 1 to 5).[6] With regard to the review questions concerning effectiveness, we also assessed the quality of the publications and assigned a level of evidence (level 1 to 5), which lead to grades of recommendation attached to the conclusions.

Results

Twenty-five publications were collected after our search was performed. Twenty-four of these publications were included for evaluation. Eleven of the included publications detailed original clinical studies (study design level 2-4),[7-17] while 13 revealed expert's opinions (study design level 5).[18-30] One original clinical study was performed in infants with moderate atopic dermatitis and was thus excluded from the results section.[31] Because of the unique nature of this last study, it will be discussed briefly further on. The publications with expert's opinions showed some overlap in content, caused by multiple publications from the same author or institution.

In which ways does the methodology of the treatment with wet-wrap dressings differ between the publications?

The methodology of WWT, as described in the 24 publications, differs with regard to nine key points, as is summarized in table 1. If we only look at the clinical studies, we find that 10 of the 11 first authors advocate the application of either cream (n=6) or ointment (n=4) directly on the skin instead of soaking the first layer of bandages in warmed up cream (n=1). When mentioned, the primary reason for direct skin application is that it would be less time consuming. (Re)wetting of the first layer of bandages was carried out with plain water in 9 out of these 10 studies and was combined with an aqueous solution of chlorhexidine in one. With the exception of one publication, describing a facial WWT with plain gauze, all the clinical studies reported the use of elasticated tubular cotton

bandages. In 9 studies they used Tubifast®, while in one study they used either Tubifast® or Tubigrip®, depending on the preference of the patients and their parents. Four of the 11 studies reported a WWT including a facial mask.

Topical product	Cream or ointment as emollients, (diluted) topical corticosteroids or a combination of both.
Type of bandages	Double layer of cotton cloth, plain cotton gauze or elasticized cotton tubular bandages (Tubigrip® or Tubifast®). A second layer of flannel instead of cotton was also reported.
Application technique of topical product	The topical product is applied directly on the skin or is warmed up and used to soak the first layer of bandages, which is then applied onto the skin.
Application frequency of topical product	Once to thrice daily.
(Re)wetting of the first layer of bandages	Once, twice, thrice or every 2-3 hours daily. Water is most commonly used but an antiseptic solution and soaking of the first layer in heated cream have been reported
Bandages left in situ	3, 6-8, 12 or 24 hours per day
Area treated	Only the extremities, the trunk and the extremities, only the face, or the entire body
Duration of treatment	Intervention treatment of 2 to 14 days.
Location of treatment	Hospitalization or out-patient treatment

Table 1
Possible differences in the methodology of wet-wrap treatment

Is the use of wet-wrap dressings an efficacious intervention treatment modality?

Ten out of 11 included original clinical studies reported data on the efficacy of a WWT in children with severe and/or refractory AD. They all used a WWT consisting of a double layer of tubular bandages or gauze, with a wetted first layer and a dry second layer. Cream or ointment was applied directly on the skin in 9 studies and soaked into the first layer of bandages in the study of Goodyear et al.[9] The details concerning the patient population, topical products, application frequency, duration of treatment and outcome parameters of efficacy are listed in table 2.

First author	Study design	Patients	Topical product	Appl.	Duration	Efficacy
Abeck D	Observational	3 children (3-12 y) 3 adults	Emollients and Chlorhexidine solution	3dd 2dd	24 h/day 3 days	SCORAD index
Devillers ACA	Observational; inpatient comparison	14 children (6 m-10 y) 12 adults	Diluted (5-25%) FP cream	1dd	24 h/day 6-9 days	Modified objective SCORAD
Goodyear HM	Observational	30 children (9 m-2 y)	HCA 0.5% (<2 y) Diluted (10%) BV cream (>2 y)	2dd 2dd	24 h/day 2-5 days	IGA
Mallon E	Observational	21 children (4 m- 10 y)	HCA 0.5% (<2 y) Diluted (10%) BV cream (>2 y)	1dd 1dd	24 h/day Up to 5 days	IGA and parental questionnaire
Oranje AP	Observational	3 children (6 m-4 y) 4 adults	Diluted (50%) FP cream	1dd	24 h/day 14 days	Modified objective SCORAD
Pei AY	Randomized controlled	40 children (1-15 y)	Diluted (10%) FP ceram vs. Diluted (10%) MF ointment	1dd 1dd	8 h/day 14 days	CSS and parental questionnaire
Schnopp C	Randomized controlled; inpatient comparison	20 children (2-17 y)	MF ointment vs. vehicle	2dd 2dd	16 h/day 5 days	Regional SCORAD and TEWL
Tang WY	Observational	12 children (3-12 y)	Diluted (10-15%) MF ointment	1dd	12 h/day 14 days	CSS and self assessment
Tang WY	Observational	10 children (4-15 y)	Diluted (10%) MF ointment	1dd	3 h/day A few days	IGA and parental questionnaire
Wolkerstorfer AW	Observational; comparison	31 children (5 m-13 y)	Diluted (5-50%) FP cream	1dd	24 h/day 14 days	Modified objective SCORAD

Table 2
Clinical studies on the efficacy of wet-wrap treatment
FP= Fluticasone propionate; HCA= Hydrocortisone acetate; BV= Betamethasone valerate; MF= Mometasone furoate; dd= times per day; SCORAD = SCORing Atopic Dermatitis; IGA = investigator global assessment; CSS = unspecified clinical scoring system; TEWL = trans epidermal water loss

Efficacy was scored using different clinical scoring systems. The SCORAD index was used in one publication. This system combines the extent (A) and intensity (B) of skin lesions with subjective scores on itch and sleeplessness (C).[32] Three publications used the modified objective SCORAD (A and B) and 1 publication used a regional SCORAD (B). Unclassified clinical scoring systems (CCS) were used in 2 and investigator global assessments (IGA) in 3 studies. Additional parameters included transepidermal water loss (TEWL) measurement, parental questionnaires aimed at the subjective assessment of the impact of AD on daily life and similar patient or parent assessments obtained during an interview.

Although the methodology varied with regard to several other previously mentioned key points, all studies reported a successful intervention treatment of 2-14 days, with an improvement of AD skin lesions (evidence level 4). This is in concordance with the stated expert's opinions and our own experiences, which describe WWT as a successful intervention treatment in children with severe and/or refractory AD (evidence level 5).

Is the use of wet-wrap dressings with (diluted) topical corticosteroids more efficacious than the use of wet-wrap dressings with emollients or emollients in combination with antiseptics?

Several experts describe a successful WWT with emollients only, usually in patients with milder but still extensive skin disease.[18,19,20,22,28,29] However, WWT using (diluted) topical corticosteroids is generally regarded as being more efficacious, which is in concordance with our own experiences (evidence level 5). The available data from the 2 clinical studies detailed below supports this notion, although the number of included patients is small (evidence level 4).

Schnopp et al reported a controlled trial in which they performed a WWT on both arms of 20 patients.[14] They used mometasone furoate 0.1% (MF) ointment on one side and its vehicle on the other side. After 3 and 5 days the severity of AD lesions improved on both sides, with a significantly better improvement of the regional SCORAD scores on the MF treated sides compared to the vehicle treated sides.

Wolkerstorfer et al performed a pilot study on the influence of corticosteroid dilution on the efficacy of WWT.[17] They report an impressive improvement in the modified objective SCORAD scores after 1 week of treatment, irrespective of the dilution of fluticasone propionate 0,05% (FP) cream used (5%, 10% or 25%). Two patients were treated with the same methodology, using emollients instead of diluted FP cream. They only showed a minor improvement. The improvement in objective SCORAD scores in their study was related to the absolute amount of applied corticosteroid per m2 body surface. This

curve levelled out at approximately 800 μg/m2 body surface, above which efficacy hardly increased further.

No statements can currently be made on the efficacy of a WWT using emollients and antiseptics as compared with (diluted) corticosteroids or emollients alone. Abeck et al published a clinical study detailing a WWT with application of emollients thrice daily combined with chlorhexidine 0.5% solution twice daily to wet the first layer of bandages.[6] Their treatment was efficacious, showing an improvement of the SCORAD index from 56.9 (±5.6) to 32.4 (±1.5) after 3 days of treatment (evidence level 4). However, a direct comparison of these results with studies using (diluted) corticosteroids or emollients alone is not possible due to differences in methodology and outcome measures.

Is the use of wet-wrap dressings with diluted topical corticosteroids a safe intervention treatment modality?

When using wet-wrap dressings with (diluted) topical corticosteroids the primary safety concern is systemic bioactivity of the corticosteroids. Six of the clinical studies included safety parameters intended to detect systemic bioactivity, as detailed in table 3.

Measurements of early morning serum cortisol (EMSC) and urinary cortisol/creatinine ratio (UCCR) before and after treatment have shown a temporary decrease of the values during treatment periods of 2-14 days (evidence level 4). Goodyear et al found profound decreases of EMSC levels below the detection level in all their patients after 2-5 days of treatment.[9] Two weeks after completion of the active therapy their values had normalised. The publications of Wolkerstorfer et al and Devillers et al showed that the risk of EMSC levels dropping below the lower reference value could be decreased by once daily application and further dilution of the topical corticosteroids to 10% or even 5% of their original strength (evidence level 4). [8,17] Prolonged suppression of the hypothalamus-pituitary-adrenal-cortex axis has not been reported after short-term intervention treatment. Devillers et al reported one adult patient with a prolonged suppression after a long-term treatment at home, with an average follow-up of 17 weeks (11-41).[8] He also used concomitant corticosteroids via inhalation. One of the most important clinical symptoms of systemic bioactivity of corticosteroids in children is growth retardation. McGowan et al looked at short-term growth and bone turnover during wet-wrap treatment with diluted corticosteroids in 8 children with a median age of 5.1 (3.3-8.8) years.[11] They used knemometry to measure lower leg length growth rate and urinary deoxypyridinoline crosslink excretion corrected for creatinine excretion to measure bone and collagen turnover. There were no significant differences found between the outcomes before and during a median treatment period of 12 (2-18) weeks.

Reference	Study design	Patients	Topical product	Appl.	Duration	Safety
Devillers ACA	Observational; inpatient comparison	14 children (6 m-10 y) 12 adults	Diluted FP cream	1dd	24 h/day 6-9 days	Early morning serum cortisol
Goodyear HM	Observational	30 children (9 m-2 y)	HCA (0.5%) cream (<2 y) Diluted BV cream (>2 y)	2dd 2dd	24 h/day 2-5 days	Early morning serum cortisol
McGowan R	Observational	8 children (3.3-8.8 y)	Diluted BD	1dd	24 h/day Up to 14 days	Knemometry and urinary Deoxypyridinoline crosslink excretion
Oranje AP	Observational	3 children (6 m-4 y) 4 adults	Diluted FP cream	1dd	24 h/day 14 days	Early morning serum cortisol
Tang WY	Observational	12 children (3-12 y)	Diluted MF ointment	1dd	12 h/day 14 days	Early morning serum cortisol
Wolkerstorfer AW	Observational; comparison	31 children (5 m-13 y)	Diluted FP cream	1dd	24 h/day 14 days	Early morning serum cortisol and urinary cortisol/creatinine ratio

Table 3
Clinical studies into the safety of wet-wrap treatment with (diluted) topical corticosteroids
FP= Fluticasone propionate; HCA= Hydrocortisone acetate; BV= Betamethasone valerate; BD= Beclomethasone Dipropionate; MF= Mometasone furoate; dd= times per day

Table 4 lists reported adverse events other than systemic bioactivity in both clinical studies and expert's opinions. Unfortunately only 4 of the 11 clinical studies report percentages on some of these adverse effects.[8,9,10,15] We decided to assign each event to a different risk factor group, stating the frequency as rare, common or frequent. The assignments were made on the basis of the limited available data on percentages and our own personal experience.

Adverse event	Occurrence
Discomfort including chills and poor acceptance	Frequent
Folliculitis	Common
Refractory skin lesions on the areas not covered by bandages	Common
Impetigo	Rare
Cutaneous Pseudomonas aeruginosa infection	Rare
Herpetic infections	Rare

Table 4
Reported complications, besides temporary systemic bioactivity, during an intervention treatment with wet-wrap dressings and (diluted) topical corticosteroids for a maximum period of 14 days.

Discussion

This review confirms our initial suspicion regarding the wide variety in methodology with regard to WWT. Based on the available data and our own experiences we would like to make some general remarks with regard to future standardisation of treatment.
Most authors, including ourselves, advocate application of cream or ointment directly on the skin instead of soaking the first layer of bandages in heated cream. Preparation time can thus be reduced, while good efficacy is maintained. Application frequencies of up to 3 times per 24 hours have been reported during use of emollients. Using diluted topical corticosteroids is more efficacious than using emollients only. However, using diluted topical corticosteroids warrants once daily application, because of the risk of systemic bioactivity. Which topical corticosteroid should be used and to what degree it should be diluted is still uncertain. The most commonly reported products used are 10% dilutions of potent corticosteroids.[9,10,13,15,16] The studies from Wolkerstorfer et al and Devillers et al confirmed a good clinical efficacy and safety of WWT using a 10% dilution of FP cream.[8,17] They also reported good results with a 5% dilution, which might indicate that further dilution without loss of efficacy is possible. At this moment a 10% dilution seems to provide adequate efficacy and safety and is a good starting point for further studies. Advocating the use of fluticasone propionate or mometasone furoate above other moderately potent corticosteroids is based on their known pharmacological properties and is another issue in need of further investigation.

In theory, all closefitting cotton bandages can be used in WWT. Tubifast® elasticated tubular cotton bandages are currently the most commonly used. In 2003 Tubifast Garments® were introduced onto the market. This product line includes long sleeved shirts, pants, socks and gloves in different paediatric sizes. They are made from similar material as the original Tubifast® and can be washed and reused up to 20 times according to the manufacturer. Using the garments facilitates the treatment and may save a considerable amount of time during the preparation and application phase of the treatment. The use of a facial mask during a WWT is possible and can have good clinical results.[8,12,16,17] However, one should always keep in mind the psychosocial consequences of wearing a mask and the fact that not all children and/or parents will accept their application. Their use should be discussed separately with patients and their parents when WWT is considered.

Different strategies were reported regarding application time of the bandages, ranging from 3 to 24 hours a day. Longer application times are probably more efficacious, although there is no clear evidence to support this. In a hospital setting a 24-hour treatment schedule is feasible and in our opinion advisable. This is more difficult when patients are treated on an outpatient basis and schedules have to be incorporated into daily life. Intervention treatments of 2 to 14 days have been published in clinical studies. With use of (diluted) topical corticosteroids, we would like to advocate an intervention treatment with a maximum of 7 days. This period is consistent with the study of Wolkerstorfer et al, who reported substantial improvement during the first week of treatment with little further improvement in the second week, and with the strategy of most authors, who describe good clinical efficacy with treatment periods of up to 1 week (table 2). [17]

WWT, especially when combined with (diluted) topical corticosteroids, is a very efficacious intervention treatment in children with severe and/or refractory AD. Unfortunately it is also a very laborious and time-consuming treatment modality that calls for close supervision. Use of topical corticosteroids involves the risk of systemic bioactivity and the different parameters influencing this risk should be considered. Several possible risk factors for systemic bioactivity during WWT with diluted corticosteroids were suggested, including the type of corticosteroid, the dilution, twice daily versus once daily application, inter-individual differences between patients and the use of concomitant corticosteroids, for instance via inhalation. Four of the 6 clinical studies summarized in table 3 propagated the use of a "new generation" topical corticosteroid, either fluticasone propionate or mometasone furoate. These products claim a potent local effect with relatively low systemic absorption, which in theory should be beneficial for further

reduction of systemic bioactivity during wet-wrap treatment with diluted corticosteroids. However, a controlled trial comparing the use of these products versus the older topical corticosteroids in a WWT is lacking.

Other adverse events are usually mild and temporary but should also be considered. The reported discomfort is mostly due to chills after application of the first moist layer of bandage, warranting close attention to the temperature of the water. Induction of folliculitis is probably due to the occlusive effect of the treatment and may be reduced by using creams instead of ointments and application of the topical product in the direction of hair growth. Whether or not there is an increased risk of impetigo or herpetic skin infections is still unclear. Both events are well known complications in children with AD without WWT. Secondary skin infections with Pseudomonas aeruginosa appear to be rare, but are possibly due to the moist environment induced by the bandages. Insufficient cleaning of the water sprayers used to rewet the first layer of bandages may constitute a cause of infection. Although striae have not been reported during a wet-wrap intervention treatment, they were observed during a long-term intermittent treatment.[8] Because children entering puberty are already at risk of developing striae, we consider this age group to have a relative contraindication against WWT. Cost-benefit ratios of WWT were not included in this review, but seem to be lacking at the moment.

We believe that WWT should be reserved for second line intervention treatment in patients with AD who have failed to respond to conventional treatment schedules. This is in concordance with a publication from Goodyear and Harper, who advocated caution in the use of WWT for atopic dermatitis.[21] Further support is found in a recent publication from Beattie and Lewis-Jones, who performed a pilot study comparing a WWT with hydrocortisone acetate cream to the use of hydrocortisone acetate cream twice daily without wet-wrap dressings.[31] Both patient groups consisted of children with moderate AD. No significant differences in clinical efficacy scores or quality of life scales were found between the two groups and the authors concluded that WWT should not be considered as a first line treatment in mild to moderate atopic dermatitis.

This review shows an overview of the currently available evidence for the use of WWT as an intervention treatment in children with severe and/ or refractory AD. Although the reported clinical studies started with a study design ranging from level 2 to 4, the resulting evidence levels did not exceed level 4. This was mostly due to the small numbers of included patients, which together with the different methodologies of the clinical studies forms the main weakness of this review. Presently we need large prospective studies to evaluate the efficacy and safety profile of WWT as an intervention treatment in children with severe and/or refractory AD. In addition to standardized clinical efficacy and

safety parameters, these studies should also include quality of life assessments and cost-benefit ratios as outcome parameters. These studies are necessary for further standardization of the methodology and should focus on the use of diluted topical corticosteroids versus emollients and the comparison of WWT with more conventional treatment modalities.

Recommendations

Based on the available data we were able to formulate the following conclusions with a grade C of recommendation.

1. WWT using cream or ointment and a double layer of cotton bandages with a moist first layer and a dry second layer, is an efficacious short-term intervention treatment in children with severe and/or refractory AD.
2. The use of wet-wrap dressings with diluted topical corticosteroids is a more efficacious short-term intervention treatment in children with severe and/or refractory AD than wet-wrap dressings with emollients only.
3. The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD, with temporary systemic bioactivity of the corticosteroids as the only reported serious side effect.
4. Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution of the product can reduce the risk of systemic bioactivity.

We would like to stress that the success of WWT depends on adequate training of patients and parents in the methodology of the treatment. In our opinion a skilled dermatological nurse is invaluable in this process.

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Treatment of patients with atopic dermatitis using wet-wrap dressings with diluted steroids and/or emollients. An expert's opinion and review of the literature

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Background

The use of dampened bandages to reduce inflamed eczema (synonyme dermatitis) is an old remedy. In order to evaluate the current indications for so-called wet-wrap treatment (WWT) for atopic dermatitis (AD), and to compare the different currently recognized methods, a group of experts critically reviewed their own expertise on WWT in respect to the existing literature on the subject.

Results

WWT is well tolerated in eczema due to the cooling effect on the skin and the rapid improvement in skin inflammation. It has been shown to be an extremely effective treatment for acute erythrodermic dermatitis, therapy-resistant AD and intolerable pruritus. Advantages of WWT include rapid response to therapy, reduction in itch and sleep disturbance, and potential for reduction in usage of topical corticosteroids (TCS). However, disadvantages include high cost, the necessity for special training in usage, potential for increased TCS absorption, increased cutaneous infections and folliculitis, and poor tolerability. Precautions to reduce the risks of long-term treatment should include education, monitoring of weight and height and, if necessary, serum cortisol levels. In adolescents the risk of striae from TCS absorption around puberty is high, and WWT with TCS in this age group should be used as a short-term therapy only and with extreme caution. To reduce risks, dilutions of steroids may be used ranging from 5 to 10%. In the maintenance phase this treatment can be rotated with the use of emollients only. Low potency TCS should be used on the face (with a mask).

Conclusion

WWT using diluted steroids is a relatively safe addition to the therapeutic treatment options for children and adults with severe and/or refractory AD. Explanation and education is extremely important in the treatment of AD and WWT should only be employed by practitioners trained in its use. Specialized nursing care is essential, especially when using WWT for prolonged periods.

Introduction

Atopic dermatitis (AD) is an inflammatory, chronically relapsing and pruritic skin disease. There is considerable discussion about nomenclature (atopic eczema, atopic dermatitis, constitutional eczema, extrinsic and intrinsic atopic dermatitis, atopiform eczema and atopic eczema/ dermatitis syndrome) and there is no consensus regarding the method for evaluation of the severity of the disease (SCORAD, SASSAD EASI, POEMS, etc.) and the role of IgE.[1,2] Epidemiological work has shown that the incidence of atopic dermatitis is rising in most 'westernized' countries although the majority of AD is mild to moderate in severity. Only around 10% have a modified objective SCORAD (SCORAD index not including subjective symptoms) severity of more than 40, indicating severe AD.[3]

Topical corticosteroids (TCS) and emollients are the key players in the therapy of AD. Promising drugs such as the calcineurin inhibitors, tacrolimus ointment or pimecrolimus cream have recently become available. In severe childhood AD, photo(chemo)therapy, systemic corticosteroids and immunosuppressive drugs have relative contraindications because of the potential for serious side-effects. These modalities are used only in selective cases. For patients with severe AD, agents such as tacrolimus ointment or pimecrolimus cream are not efficacious enough in most cases. In children and adults where systemic treatment is not appropriate, intermittent treatment with wet wraps (WWT) and (diluted) topical corticosteroids and emollients is an ideal option.

The role of WWT has been a matter of debate over the past 5 years. Wet-wrap dressings have been popular in the UK since 1991.[4] Earlier use can be dated back to the 1970s in the UK and even earlier in Australia (M Rogers, Children's Hospital, Sydney, personal communication). In order to evaluate the current indications for WWT, a group of experts in paediatric dermatology, with experience of the treatment modality, critically reviewed their own experience and the existing literature on the subject.

Methods

Experts in the field of atopic dermatitis in children discussed the therapeutic position of wet wraps with diluted steroids and/or emollients in meetings in Malta (2003), Rotterdam (2003), Frankfurt (2004) and Budapest (2005). All participants shared their own experiences on WWT methods; the use of water (or just emollients), types of dressings and bandages and other nursing aspects, choice of TCS and their dilution (or not), and any differences in WWT between children and adults. The pros and cons of WWT, indications for its use and precautions to reduce side-effects were considered and compared with the experiences found in the literature.

Water and dressings

Wound healing is a complex process influenced by many intrinsic and extrinsic factors. From sesame oil used by the Babylonians in 2250 BC and honey used by the Egyptians in 2000 BC to the currently available dressings, the evolution of wound products has been tremendous. Some factors influencing wound healing have been elucidated, while others are still to be discovered. The ancient Babylonians and Egyptians observed that covered moist wounds heal more rapidly than open dry wounds, but it took until 1958 for Odland to first describe that a blister healed faster when left unbroken.[5] Since then many studies have demonstrated the beneficial effect of a moist environment on wound healing.[6]

In a disease such as AD the skin barrier is impaired and significant amounts of water are lost through the skin.[7] In AD lesional skin a significant decrease in ceramides 1 and 3 has been found compared with the skin of healthy subjects.[8] Non-lesional skin of patients with AD also exhibits similar decreases of ceramides, in particular ceramide 1. This may be due to the fact that the epidermal enzyme sphingomyelin deacylase is expressed at high levels in the epidermis of AD patients, leading to an abnormal accumulation of sphingosyl phosphorylcholine but low levels of ceramide.[9] However, the biological and genetic mechanism behind this high expression remains to be elucidated. A second reason for dryness of the skin in AD is the diminished water binding in the stratum corneum due to a depletion of hydrophilic molecules such as natural moisturizing factor, probably due to a decrease in fillagrin. Finally, sebaceous secretion is also lower than normal in AD patients. Sebaceous glands in the dry skin of AD are reduced in number and size compared to those in the skin of normal individuals, and the lipids in sebaceous gland secretion are also reduced compared to normal subjects.

The benefit of emollients in AD may be explained by the restoration of the epidermal barrier, which prevents the penetration of allergens, irritants and organisms and breaks the itch-scratch cycle, thereby reducing the release of inflammatory mediators.[10] Wet dressings support the rehydration of the skin and afford cooling of the skin through evaporation. This gradual cooling has an anti-inflammatory effect and reduces itching. The hydration and occlusion provided by the wet wraps also increases the absorption of topical medications. These dressings also act as a mechanical barrier against scratching, allowing more rapid healing of excoriated lesions and protection against external factors such as allergens and bacteria, although heavily infected eczema may be worsened by the occlusion.

The use of wet dressings in AD generally encompasses a layer of wet tubular cotton gauze bandages, of which there are several commercial types available, covered by a corresponding layer of dry bandaging. The literature on the appropriate use of water in this approach is limited. Advice is usually given to put the bandages in lukewarm water, squeeze the water out of the bandages and then apply.[11] Nothing is said about the mineral content of the water, which may be an important consideration. Recent studies have shown that barrier recovery measured by the improvement of transepidermal water loss towards normal is inhibited by high extra cellular Ca^{++} and K^{+}, and accelerated by low extracellular concentrations of these ions.[12] Another study evaluated the efficacy of cool compresses in the treatment of experimentally induced irritant contact dermatitis with both distilled water and a physiological salt solution. It was shown that cool compresses of distilled water or a physiological salt solution improved barrier function and reduced inflammation with no statistical differences between the efficacy of the saline or water compresses.[13]

The temperature of the water used for wet wraps is also an important factor to consider, and the water should be at body temperature. If the water is too cold vasoconstriction is soon followed by secondary vasodilation. If too hot, vasodilation occurs with increased pruritus. Besides the hardness and the temperature of the water, several other mechanisms such as osmolarity and pH may account for the irritancy of water. Occlusion per se also changes the physiology of the skin and may trigger the activation of potentially active substances.[14]

Definition of wet-wrap treatment (WWT)

The use of dampened bandages is commonly used throughout the UK, Hamburg (Germany), Munich(Germany), in Rotterdam (Holland) and in several other centres. All these treatments are called wet wraps.

In the 1970s several UK centres used single layer tubular bandages or dampened cotton T-shirts and emollients with or without topical corticosteroids (TCS) to control widespread AD. An initial report in 1991 of two-layer bandaging wet-wrap therapy (WWT) described the use of Tubegauz® impregnated with hydrocortisone cream, with a dry layer on top.[4] In this "London" method for inpatients no water at all is used.

Other practitioners in the UK use water-dampened bandages with dry bandages on top. This is also the case in the 'Rotterdam' method, where the skin is re-wetted every 2 h during the day. The skin dries within 30 min and is relatively dry till the next re-wetting action (without applying emollients) 90 min later.[11,15,16]

The use of dampened bandages to reduce inflammation is an ancient medical remedy and is often used for the treatment of AD. Their use has been described as early as in ancient surgical textbooks. In his description of wound dressing, Liston writes in 1846: 'water dressings had been applied to sores for time immemorial'. In modified applications they continue to be part of approved therapy for acute inflammatory states, ulcers and other skin affections.[17]

Figure 1
Old style wet wraps (on courtesy of Dr. M. Rogers)

Details of the four major methods of WWT

Wet wraps (simple) for cooling

A wet wrap originally consisted of a cloth soaked in water and applied directly to the affected skin, usually in several layers. White lint, linen or cotton cloth was formerly used. Nowadays a variety of single-use gauze pads are available that can be fixed by a gauze bandage to the diseased skin and soaked when required with aqueous liquids. The effect is cooling, anti-inflammatory and itch reducing.[18] These positive properties of the evaporation of water from the dressing are, however, accompanied by a drying out of the skin, which makes the procedure theoretically, unsuitable for dry skin conditions like AD.

One layer wet wrap with ointment

To avoid the undesired desiccation of the skin, a modified procedure came into use for eczematous conditions, the 'oil wet wrap' ('fett-feuchte Umschläge'). First, an ointment is spread generously onto the skin. Then a bandage, soaked in lukewarm tap water and squeezed out to leave it damp is applied over it. For extensive skin affections damp pyjama cloth can be used instead of bandages. 'The effect is the same as with wet wraps, without the side-effect of drying out the skin'.[18] However, ointment enhances the risk of folliculitis.

Double-layer wet wrap with ointment or cream and water

While the damp 'pyjama' technique was conceived for in-hospital use, another modification more suitable for application at home was described in the nineties[19] and used in Australia (M Rogers, Children's Hospital, Sydney, personal communication), Dundee, Hamburg, Rotterdam and for out-patients in London (Table 3). A damp tubular bandage is applied over the ointment layer, as in the oil-wet wrap, followed by a second layer of dry tubular bandage. The second bandage layer results in a more gradual evaporation of the water from the wet bandage and therefore in a prolonged effect of moisturization and cooling.[11,19]

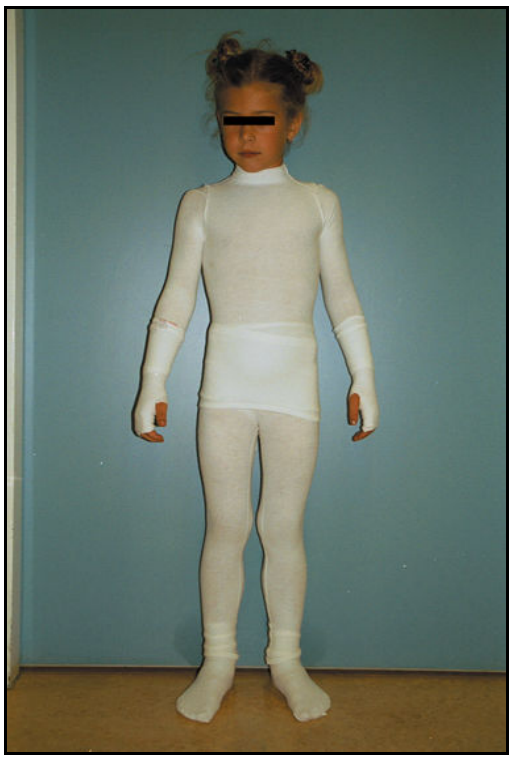

Figure 2
Tubifast pyjama for WWT.

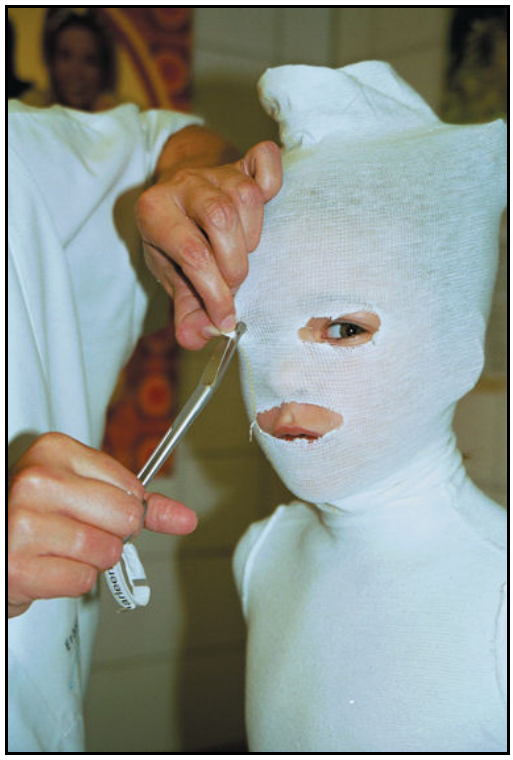

Figure 3
Preparing for the mask.

Double layer wrap with ointment alone

In 1991, Goodyear *et al.*[4] described another technique for the treatment of AD in children, which they termed 'wet-wrap dressings'. The crucial difference with this method is that no water is applied to the bandages. The 'wetness' results from diluted steroid cream, which becomes more fluid when warmed by immersion in hot water. The bandage is soaked in the warm cream and applied to the skin after a bath with oily additive. Finally, a second layer of dry tubular bandage is wrapped around.

All of the authors publishing reports on wet-wrap dressings describe a 'cooling effect on the skin'. [4,11,15,16]

Wet-wrap treatment in children with atopic dermatitis

The first detailed reports about the use of diluted topical steroids and 'wet-wrap' dressings in patients with AD were centred on the treatment of children.[4,11] They described a very successful intervention treatment for severe and/or refractory skin disease with a relatively good safety profile. Patients showed a marked improvement of their skin lesions associated with a significant decrease in objective SCORAD scores during a clinical treatment period of 1 week.[15,16]

In the Erasmus MC–Sophia Children's Hospital (Rotterdam), the treatment is commonly started as whole body application and continued throughout a short hospitalization of 7 days. After patients have been discharged from the hospital, the treatment is continued at home for seven consecutive days on involved areas, and thereafter for only 4 days per week (Table 1). Monitoring for potential side-effects is undertaken throughout the therapy by measuring fasting early-morning serum cortisol and growth parameters. Topical corticosteroids have a well-known potential for systemic and local side-effects. Young children are especially at risk for systemic absorption due to their low body volume to skin surface area ratio compared to adults. If systemic absorption occurs, suppression of the hypothalamus-pituitary-adrenal gland (HPA) axis and growth retardation may result. Evaluation of the adverse effects in the published data reveals that temporary suppression of the HPA axis has been reported as a possible side-effect of using diluted topical steroids and wet-wrap dressings.[11,15,16] A local side-effect that may occur more easily in childhood than in adulthood is the development of striae, particularly in pubertal children (figs 1, 2 and 3).

1.	Choose the appropriate width of the tubular bandages and cut these to size to fit the arms, legs and trunk. Cut a facial mask if necessary. Instead of bandages, tubifast garments are used since 2004.
2.	Apply the appropriate dilution of fluticasone propionate 0,05% (FP) cream on the skin *Diluted steroids in emollients of 1:19 (face, body in infants) and 1:9 (body) or 1:3 (body) are used.*
3.	Wet the individual pieces of tubular bandage in lukewarm water. When garments are used, then the inner garment is wetted using a plant spray
4.	Apply the first layer of wet tubular bandage. Connect the arm and leg pieces to the trunk. *When garments are used, then the inner garment is wetted using a plant spray* Use the facial mask if necessary.
5.	Apply the second layer of dry tubular bandage. Again connect the arm and leg pieces to the trunk. Use the facial mask if necessary. *When garments are used, then a second dry garment is pulled over the wet one*
6.	Re-wet the bandages/ *or the inner garments* every 2 to 3 hours.
7.	Repeat the above mentioned procedures daily.
8.	After 7 days of treatment the diluted FP cream is only applied on the clinically involved skin for 4 of 7 consecutive days of the week. Emollient is applied on the uninvolved skin. Patients can perform the treatment at home.

Table 1.
Wet wraps treatment according to Oranje with recent modification (printed italic) (1999). Since 2004 tubifast garments are used. (guidelines Erasmus medical center – Sophia children's Hospital)

Using greater dilutions of the topical steroid (1:20 and 1:10) reduces the risk of systemic bioactivity, while maintaining a good efficacy.[15,16] Fortunately, growth retardation as a result of WWT has not been described. This finding is supported by McGowan *et al.*, who did not observe any growth retardation in a group of eight children during a median period of 12 weeks of WWT.[20] They measured velocity of lower leg length growth using knemometry, and assessed bone and collagen turnover by urinary deoxypyridinoline crosslink excretion corrected for creatinine excretion. However, this is a small group, and sensitivity to TCS absorption appears to be very variable.

In Rotterdam, diluted fluticasone propionate (FP) 0.05% cream (1:4, 1:10 and 1:20) is used once daily.15,16 FP cream and mometasone furoate are newer, potent topical corticosteroid agents, which have been shown to have an improved benefit/risk ratio with relatively low systemic absorption and may further lower the risk of steroidinduced side-effects. However, there is still a risk of skin atrophy.[15,16] Currently, the use of 1:20 dilutions of FP cream is advocated in children under 2 years of age and dilutions of 1:4 and stronger are strongly discouraged. Parameters of systemic bioactivity, such as fasting early morning serum cortisol levels should be monitored (i.e. checked before the first day of start therapy, after 1, 3, 4, 6 consecutive weeks each and then every 2–3 months).

Oranje and coworkers (unpublished data) observed an initial impressive improvement after 3 to 7 days, but after 4 weeks worsening and stabilizing of AD to mild to moderate severity was observed. We call this the 'broken stick effect' (fig. 4).

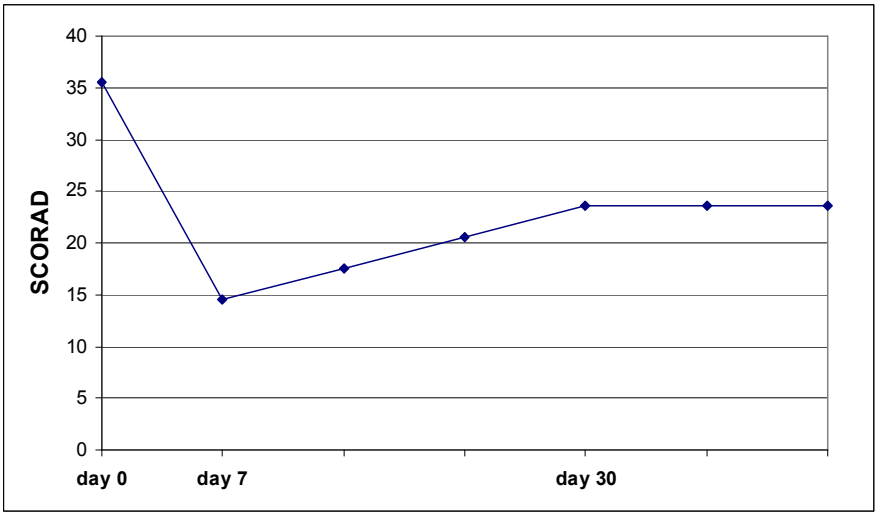

Figure 4
Double-broken stick phenomenon in objective modified SCORAD evaluation. Retrospective study in 48 children with AD treated with wet-wrap dressings with diluted FP cream in the period 2001-2004 (Willems M, Oranje AP, unpublished data).

In Hamburg (department of dermatology) the treatment is as an alternative to hospitalization and is conducted in a daycare clinic for 3 to 5 days. Patients are instructed by trained nurses to perform double layer wet dressings with the tubular bandage at home, using diluted steroid creams only on affected areas and emollients on the rest of the skin (B Kunz, personal communication).

At Great Ormond Street Hospital (GOSH), babies under 1 year of age are treated with 0.5% hydrocortisone cream and children over 1 year with betamethasone valerate 0.01% cream (Betnovate® diluted 1:10) and using Tubegauz bandages. Either aqueous or cetomacrogol cream can be used as the diluent (Tables 2 and 3).[4]

ACTION	RATIONALE
Treatment Procedure	
Cut appropriate sized pieces of the cotton tubular bandage [Tubigauz®] for the arms, legs and trunk	The technique comprises 2 layers of bandaging
Soak the individual pieces of Tubigauz®] (suit1) in the steroid ***cream*** [1] (not water)	To produce the first "wet" layer
Put on the first layer of "wet" Tubigauz®]; tie the arm and leg pieces to the trunk	This enables all affected areas on the limbs and trunk to be covered by a dressing impregnated with a weak steroid cream
Then apply the second "dry" suit over the top of the wet layer securing the arm and leg pieces to the trunk section	This completes the dressing
Keep hands covered. If the child is a thumb-sucker a small hole can be cut in the bandage.	To minimise damage from scratching
Treatment regimen	
Dressings are changed twice daily by the nursing staff for usually 3 days	There is usually a rapid improvement and in most cases >90% clearance of eczema in this period of time.
Apply separate topical preparation to face and neck as prescribed.	Areas not covered by the wet dressings
Treatment immediately after the application of wet dressings	
The child is kept in hospital for a further one to two days and the residual or recurrent areas of eczema treated with an appropriate topical steroid ***ointment*** [2] (without the use of dressings) once or twice daily, as needed	Treatment during this time is then continued after discharge from hospital at home. It allows for the skin condition to stabilize.
The use of a moisturizing agent at other times during the day to all areas of dry skin (2-3 x daily)	To maintain the integrity of the skin barrier
General measures	
Twice daily cool baths with an oily bath emollient	To cleanse and hydrate the skin
Use a soap substitute, such as aqueous cream or emulsifying ointment to wash	Normal soap too drying and can irritate the skin
If there is any suspicion of secondary bacterial infection oral antibiotics should be prescribed by the doctor[3]	Skin infection may be responsible for the exacerbation of eczema
A sedative antihistamine is also helpful in this situation and should be given as prescribed.	To help settle the child
Loose cotton pyjamas should be worn over wet dressings	To prevent child becoming cold
Discharge planning	
Educate caregivers on treatment and management at home, support with written instructions	Essential so that the control of eczema is maintained
Liase with GP and community paediatric nursing team as appropriate	To ensure child and care giver supported locally
Outpatient follow-up appointment within 2 -3 weeks	To closely monitor progress and review longterm treatment plan

Table 2
Wet wrap dressings for in-patient treatment using Tubegauz® (GOSH, London, UK)

1. Currently we use: for babies under 1yr 0.5% hydrocortisone cream and for children over 1yr betamethasone valerate 0.01% cream (Betnovate® diluted 1:10). Both hydrocortisone or Betnovate® can be diluted with either aqueous or cetamacragol cream.
2. Currently we use: for babies under 1yr 1% hydrocortisone ointment and for children over 1yr betamethasone valerate 0.025% ointment (Betnovate-RD®)
3. If there is overt impetiginization then wet dressings should be delayed until 48-72 hours after commencing antibiotics and that appropriate treatment has been confirmed from the skin swab results. If eczema herpeticum is suspected this is an absolute contraindication to the use of wet dressings.

ACTION	RATIONALE
Treatment Procedure	
Apply the weak topical steroid ointment, beclomethasone dipropionate 0.0025% (Propaderm® 1 in 10) **only** to the affected areas, including the face.	To reduce inflammation
Apply 50:50 white soft paraffin/liquid paraffin liberally to the unaffected areas	As a moisturizing agent and to maintain the integrity of the skin barrier
Apply a suit of Tubifast® bandages (one wet layer and one dry layer). Tubifast has a tighter fit compared to Tubigauz®. The wet layer uses water and needs to be kept damp using a sponge or spray	To reduce itching and prevent damage from scratching; as well as maintaining an appropriate skin temperature.
Then apply the second "dry" suit over the top of the wet layer securing the arm and leg pieces to the trunk section	This completes the dressing
Treatment regimen	
For use in hospital, dressings are changed twice daily for 3 to 5 days	This will produce a significant improvement sufficient for the child to be discharged.
Continue nightly wet wraps at home for 6-8 weeks gradually reducing frequency after this period if effective.	Stopping wet wraps abruptly can induce a flare of eczema

Table 3
Wet wrap dressings more suitable for use at home using Tubifast® (Guidelines GOSH, London, UK)
The initial assessment on admission, general measures and discharge planning are similar to that described with the other method (Table 2).

In Dundee WWT comprises the use of emollients and one, dampened layer of Tubifast® dressings with a dry layer on top. Occasionally, in severe cases, potent or moderately potent TCS are used undiluted to affected areas for a maximum of 5 days only. Otherwise, and especially in infants, 1% hydrocortisone ointment for 5 to 7 days is applied to affected areas only. WWT is only continued on a long-term basis with emollients alone, usually at night, and TCS are applied during the day without occlusion to affected areas. In a recent Dundee pilot study of 19 infants below 5 years of age with moderate AD, WWT did not prove more effective than conventional therapy with 1% topical hydrocortisone cream and emollients over a 2-week period.[21]

Long-term intermittent treatment with wet-wrap dressings and diluted corticosteroids is feasible but requires close monitoring and adequate guidance of patients and their parents.[16] Regular measurements of fasting early morning serum cortisol and growth parameters should be monitored (in long-term treatment at least every 6 to 8 weeks). For facial eczema, wearing a mask can lead to psychological resistance or problems and is refused by about 10% of the parents and/or children[22] (A Oranje, personal communication). The face is treated with WWT and more diluted steroids (1:20, 5% steroid cream) than elsewhere on the skin.[23-28] Low-potency steroid without WWT for severe facial eczema is also an option. We have now also treated a number of children with pimecrolimus 1% cream or tacrolimus 0.03% ointment for facial lesions without occlusion by a mask (A Oranje, unpublished data). The effectiveness of topical steroids may diminish

with time (tachyphylaxis) and, last but not least, the cost and time-consuming nature of the dressings limit their use.

Wet-wrap dressings in adults with refractory atopic dermatitis

Adult patients with refractory AD unresponsive to topical corticosteroids and emollient, photo(chemo)therapy and/or even systemic therapy can be treated with WWT using diluted or undiluted steroids. Treatment can be started during a short hospitalization, in an outpatient treatment centre, or as an outpatient under the supervision of a suitably trained specialist nurse. In a Rotterdam study, after 7 days of inpatient therapy with WWT and diluted FP cream (1:4 and 1:10), the WWT was continued at home daily (first week). Thereafter for four consecutive days/week (maximum five in severe cases), and for a minimum of 12 h each day, diluted FP cream was used once daily on clinically involved skin only and emollient alone was used on uninvolved skin. For the next 3 days, only emollient was applied.[16] The Rotterdam group described results of WWT using diluted FP cream (1:4 and 1:10) in seven women and five men, aged between 18 and 61 years, 3 months (average 29 years and 11 months).[16] Two patients were treated using the wet-wrap dressings including a facial mask and more diluted steroids (1:20). The remaining patients did not use a facial mask at their own request or due to absence of facial skin lesions. A marked improvement of skin lesions was noted in all patients.

One patient using prednisone orally had cortisol levels below 200 nmol/mL both before and after treatment. Only two patients developed cortisol levels below 200 nmol/mL at the end of treatment. Both used additional topical corticosteroids on the face and scalp. One patient had been treated with the less diluted and more potent concentration of FP cream (1:3) after day 5, and the other one used FP via an inhaler. This patient, who used excessive amounts of cream and also FP via an inhaler, developed prolonged hypothalamus-pituitary-adrenalcortex (HPA) axis suppression, in combination with several striae on his abdomen.

Bandages for use in wet-wrap treatment

In 1995 a paediatric nursing report described a two-layer technique using tubular stretchy bandages Tubifast®, with a wet layer, and dry layer on top, which is widely used in a variety of different methods.[4,29] This is borne out in a UK review by the British Society for Paediatric Dermatology (BSPD), which revealed wide variation in the use of emollients, water, TCS potency and dilution, and bandaging techniques. Some respondents considered cream impregnated cotton bandages to constitute WWT and some used a dry bandage technique. Recently, a number of new bandages and garments have become available. In

the UK and other parts of Europe these are Actifast® (Activa), Comfifast® (Shiloh Healthcare), Elastus Tubiquick (Most Active), Zipsocs® and Coverflex® (Hartmann); however, there may be variation in trade names and availability in other countries. Most bandages can only be washed and re-used a few times and they are difficult to apply, requiring a trained nurse and committed parents. Incorrect usage may be ineffective and potentially harmful. There are a variety of teaching videos and booklets available for parents, children and nurses. Medlock Medical now makes Tubifast® garments for WWT for varying age groups. These consist of long-sleeved roll-neck T-shirts and pull-up leggings, both with external seams to avoid irritancy. These are much simpler and easier to use and last up to 20 washes, which greatly offsets their increased cost.

Although WWT can be very beneficial for severe AD, reducing itching, improving sleep and allowing healing and therefore decreased TCS usage, it does have disadvantages. These include high cost, difficulty or intolerance of use and increased risk of cutaneous infections and systemic absorption of steroid.[29] The use of special silk clothes may be a useful addendum in the treatment of AD; however, these clothes fit less well than garments. Antiseptic activities are thought to enhance their usefulness. Coater® pyjamas are not suitable for children with AD treated with wet wraps. Coaters are made for the prevention of scratching and are especially used for children treated with steroids, emollients and tar ointments. In London (UK), Tubegauz® or Tubifast® is used and only occasionally other dressings such as pyjamas.

Comparative studies with different steroids

Apart from a few comparative studies, which have described the use of different topical treatments (steroid preparations or a steroid preparation vs. a steroid-free preparation) under wet-wrap dressings,[23,24] no comparative, methodological, evidence-based studies have been performed focusing on the technique itself. In order to define more clearly the most effective wet-wrap technique(s) in atopic dermatitis patients, such RCT studies need to be performed.

Nursing and educational aspects

Explanation and education is of fundamental importance to ensure compliance (adherence) to therapy. This should ideally be carried out by trained specialist dermatology nurses, as is the case in some UK centres or in eczema schools, which have been set up in Germany, France and Holland. It is vitally important that a nurse trained in dermatology (and paediatrics for children) assists the patient in initial demonstration of treatment and followup to avoid unnecessary side-effects and to reduce risks. Routine or

indiscriminate use of WWT in mild AD, particularly by staff untrained in dermatology, should be challenged.[25-28] In the group's experience, the most common reason for failure of WWT is non-compliance with the dressings. This is frequently a result of lack of knowledge and incorrect training by unskilled nurses or medical practitioners. High cost in terms of time and money, side-effects such as infection and folliculitis, child dislike or refusal and non-availability of dressings or creams are other important factors.

Other indications for wet-wrap treatment

Wet-wrap treatment can also be used in conditions other than AD such as:

- Guttate psoriasis with diluted steroids as crisis intervention.
- Erythrodermic psoriasis with emollients only.
- Some cases of pruritic and active urticaria pigmentosa (mastocytosis), with diluted steroids over a period of 3–6 months.
- Lamellar ichthyosis in small babies with emollients only.

Precautions and contraindications

One aspect of potential concern is systemic absorption and hypothalamic-pituitary-adrenal axis (HPA) suppression. Concerns regarding possible systemic and topical toxicity have limited the use of moderate-potency corticosteroids in children.[30] Goodyear *et al*. found that even 5 days of topical hydrocortisone cream and WWT in infants resulted in some suppression of the HPA, and proposed caution in the use of TCS under WWT.[4] The relevance of systemic absorption clearly depends on the amount of topical steroid used, the frequency of treatment, and close monitoring if used at home.

If there is overt impetiginization, then wet dressings should be delayed until 48–72 h after commencing antibiotics and confirmation of appropriate treatment by skin swab results. If eczema herpeticum is suspected this is an absolute contraindication to the use of wet dressings.[29]

Other problems encountered especially in home use include time-consuming application requiring the cooperation of the child; the frequent occurrence of *Staphylococcal* folliculitis; and the rare complication of *Pseudomonas* infection in the creases. The facial mask sometimes leads to psychological problems. We advise low-potency steroids to be used in the face. Parents also require careful instruction in the early diagnosis of eczema herpeticum.

Conclusions

A consensus on the definition of wet-wrap dressings for the treatment of atopic dermatitis (AD) can only be based on evidence and this remains to be further established. There are only limited evidence-based data demonstrating that WWT with emollients or corticosteroids are an effective therapy modality in severe AD.[31] The involved experts all agreed that wet-wrap treatment in all its different variations is effective for the treatment of severe AD. However, randomized controlled studies (RCT) studies to support this statement are currently unavailable.

It has been known for more than 35 years that wet dressings for a period of 1–3 days are highly effective for acute flare-ups of AD. Empirically, the experts concluded that in severe AD WWT with TCS is highly effective, and safer if diluted TCS are used. In the maintenance phase this treatment can be rotated with the use of emollients only. Common side-effects are bacterial folliculitis and chilling. Treatment with antiseptics under wet wraps seems to be promising, but only limited data are available.[32] The role of explanation and education is extremely important in the treatment of AD and cannot be overemphasized. Increased time spent with children and parents is in itself beneficial. Specialized nursing care is essential in long-term therapy using wet-wrap dressings. The use of TCS should be limited to short-term therapy, which may be used intermittently when necessary, provided that appropriate growth monitoring, and if necessary serum cortisol monitoring, is undertaken. Localized WWT can be used for severely affected body sites such as limbs, for example. In older children and adults, cream impregnated tubular bandages such as Zipsocs® can also be extremely useful for limbs. During long-term treatment, a step-down approach for TCS usage is essential: first week once daily, second week once daily only to affected areas, and then tapering off to only 4 days per week. WWT masks are better reserved for short-term management and are not always tolerated. and in cases where long-term TCS are necessary for the face, treatment with one of the newer topical immunomodulators may be beneficial.

In summary, whichever method is used, the effect of wet dressings can be very impressive; they can make the child feel more comfortable by rapidly reducing itching and thus improving sleep. Wet-wrap dressings are undoubtedly a valuable tool for the treatment of children with severe generalized AD. The use of a less potent dilution of FP cream or MF cream/ointment has been shown to be effective and diminishes the risk of TCS therapy. However, home use requires adequate training and motivation to ensure good compliance and must be carefully monitored, while maintaining good efficacy. A daycare centre with dermatologically qualified nurses, with appropriate paediatric training, provides an excellent setting for the follow-up of these patients.

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"Wet-wrap" treatment in children with atopic dermatitis: a practical guideline

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Treatment of children with severe atopic dermatitis (AD) can be especially challenging as several possible intervention treatments have (relative) contraindications in childhood. In recent years wet-wrap treatment (WWT) has been advocated as a relatively safe and efficacious intervention treatment in children with severe and/or refractory AD. The goal of this publication is to provide a practical guideline as a starting point for clinicians who are interested in using WWT in their own clinical practice. We will address several practical issues surrounding the use of WWT by describing our own experiences supplemented with data from the literature.

Introduction

Possible intervention treatments in patients with severe atopic dermatitis (AD) consist of photo(chemo)therapy or systemic treatments such as oral corticosteroids, cyclosporine or azathioprine. In childhood these interventions all have (relative) contraindications, which can make treatment of children with severe AD especially challenging.

In recent years wet-wrap treatment (WWT) has been advocated as a relatively safe and efficacious intervention treatment in children with severe and/or refractory AD.[1] WWT is defined as a treatment modality using a double layer of tubular bandages or gauze, with a moist first layer and a dry second layer. Despite this general definition there is still considerable variation in the reported methodology of WWT, as was described previously by us in a systematic review of the literature.[2] Important variables include the topical products and bandages used, occlusion time and treatment duration.

The goal of this publication is to provide a practical guideline as a starting point for clinicians who are interested in using WWT in their own clinical practice. We will address several practical issues surrounding the use of WWT by describing our own experiences supplemented with data from the literature. The methodology described below is the one that has been used over the last years in the Pediatric Dermatology unit of the Erasmus MC – Sophia Children's Hospital in Rotterdam, the Netherlands.[3] The treatment protocol is summarized in table 1 and will be described in more detail below.

1.	Choose the appropriate size Tubifast Garments® to fit the arms, legs and trunk. Cut a facial mask from the appropriate size Tubifast® if necessary.
2.	Apply the appropriate dilution of fluticasone propionate 0,05% (FP) cream on the skin
3.	Wet the individual pieces of tubular bandage in lukewarm water.
4.	Apply the first layer of wet tubular bandage. Use the facial mask if necessary.
5.	Apply the second layer of dry tubular bandage. Again use the facial mask if necessary.
6.	Re-wet the bandages every 2 to 3 hours. Rewetting is stopped during the night
7.	Repeat the above mentioned procedures daily.

Table 1

Summarization of the WWT protocol as it is currently used in the Pediatric Dermatology unit of the Erasmus MC – Sophia Children's Hospital in Rotterdam, the Netherlands

Patient selection based on severity of atopic dermatitis

WWT was originally developed as an intervention treatment for children with widespread and severe AD.[4] Although its use has been spreading, we believe WWT should still only be used in this select group of difficult to treat patients. This view is supported by recent publications that have stressed that WWT treatment should be reserved as a second line treatment and is not to be used as a first line treatment in AD.[5,6] In Rotterdam we only select patients over the age of 6 months with severe AD as is reflected in an objective SCORAD score of 35-45 or more.[7] This scoring system combines the extent of the skin lesions with the intensity of six clinical features of AD. Next to a lower age threshold of 6 months we also maintain an upper age threshold at the start of puberty, which is usually around 11 years of age. We consider puberty a relative contraindication for the treatment due to the a priori increased risk for striae distensa at this age.

Materials needed in wet-wrap treatment

In our recent review we found WWT with diluted topical corticosteroids to be more effective as a short-term intervention treatment in children with severe and/or refractory AD than WWT with emollients alone.[2] The most commonly reported topical products are 10% dilutions of potent topical corticosteroids.[2] We personally advocate the use of dilutions of fluticasone propionate (FP) or mometasone furoate based on their known pharmacological properties.[8,9] Our own current product consists of a 10% (1 part : 9 parts) dilution of FP 0,05% cream in petrolatum 20% cetomacrogol cream (9 parts), which is compounded by our pharmacist. The concentration of FP cream is decreased to 5% (1 part :19 parts) if facial lesions are treated. Alternative treatment options for facial lesions without using a facial mask include low potency topical corticosteroids or topical calcineurine inhibitors. We currently prefer the last option and use pimecrolimus 1% or tacrolimus 0.03% ointment.[10]

Any type of close fitting cotton bandages could in theory be used in a WWT. We have always used Tubifast® elasticised tubular cotton bandage, which is also the most commonly reported brand in the literature.[2] At the moment we almost always use Tubifast Garments® , which were introduced onto the market in 2003. This product line includes long sleeved shirts, pants, socks and gloves in different pediatric sizes. They are made from similar, latex free, material as the original Tubifast® and can be washed and reused up to 20 times according to the manufacturer. Using the garments facilitates the treatment and saves a considerable amount of time during the preparation and application phase of the treatment. It also reduces the risk for refractory skin lesions on the areas not covered by bandages. If facial lesions are also to be treated in the WWT we use the original Tubifast®

to make a mask by cutting out holes for the eyes, mouth and nose. One should always keep in mind the psychosocial consequences of wearing a mask and the fact that not all children and/or parents will accept their application. In our patient population between 10-20% of children treated with WWT do not use a mask. Their use should always be discussed separately with patients and their parents when WWT is considered.

Methodology of application and (re)wetting.

Patients may be treated on an in-patient basis or via a day-care unit. If the choice is available we believe in-patient treatment is preferable due to the complex and time consuming nature of the treatment. Each day starts by bathing the patients for 5-10 minutes in lukewarm water with additional bathing oil by Balneum Hermal®. After briefly toweling the children dry the cream is then applied directly on the skin in the direction of the hair growth, to avoid occlusion of hair follicles. Subsequently the first layer of Tubifast Garments® is wetted in lukewarm water and put on the skin after gently squeezing out all excess water. This is followed by the application of a second, dry layer of Tubifast Garments® and then the patients pyjama or clothes. The second dry layer slows down the evaporation of water from the first layer and makes wearing clothes on the of the bandages more comfortable. The first layer of bandage is rewetted every 2-3 hours by peeling back the second, dry layer and spraying lukewarm water with a plant sprayer. During the night rewetting is stopped to ensure patients can sleep unobtrusively through the night.

Reported application times of the bandages range from 3 to 24 hours a day.[2] Longer application times are probably more efficacious, although there is no clear evidence to support this. In a hospital setting a 24-hour treatment schedule is feasible and in our opinion advisable. This is more difficult when patients are treated on an outpatient basis and schedules have to be incorporated into daily life, where shorter application times are often preferable.

Treatment duration

WWT interventions of 2 to 14 days have been published in clinical studies.[2] When diluted topical corticosteroids are used we would like to advocate an intervention treatment of 7 days, with a possible extension to a maximum of 14 days in severe cases. A standardized period of 7 days is consistent with the study of Wolkerstorfer et al, who reported substantial improvement during the first week of treatment with little further improvement in the second week.[11] Other authors have also described good clinical efficacy with limited treatment periods of up to 1 week.[1,2]

In very severe and recalcitrant cases one can try to use WWT for a prolonged maintenance phase by tapering off the frequency off applications. We have personal experience with using once daily applications for a maximum of 4-5 consecutive days in the week.[12] During the remaining days of the week patients are only allowed to use emollients. Evidence for this approach is lacking and we have had variable results. In general the results during a prolonged maintenance phase as described above seem to be less impressive than during a short term intervention.

Safety and possible adverse events

The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD.[2] Reported adverse events are not common and usually mild and temporary in nature. Transient systemic absorption of the topical corticosteroids, resulting in temporary early morning fasting serum cortisol levels below the detecting threshold, is the only reported serious side effect.[2] Because of this the use of diluted topical corticosteroids should be limited to once daily applications. Concomitant use of corticosteroids, for instance via inhalation, should be taken into account when starting the treatment. Measurement of early morning fasting serum cortisol before and after treatment may be used to asses systemic bioactivity. Growth retardation due to WWT treatment has not been reported.[1,2,13]

Adverse event	Occurrence
Discomfort, including chills and poor acceptance	Frequent
Folliculitis	Common
Refractory skin lesions on areas not covered by bandages	Common
Temporary systemic bioactivity of corticosteroids	Common
Cutaneous Pseudomonas aeruginosa infection	Rare
Impetigo	Rare
Herpetic infections	Rare

Table 2
Possible adverse events during an intervention treatment with wet-wrap dressings and (diluted) topical corticosteroids for a maximum period of 14 days.

Other possible adverse events are listed in table 2. Discomfort is most frequent and almost invariably due to chills after application of the first moist layer of bandage. This can be reduced by closely monitoring the temperature of the water used. Induction of folliculitis is probably due to the occlusive effect of the treatment and may be reduced by using creams instead of ointments and application of the topical product in the direction of hair growth. This occlusive effect of ointments is the main reason we use a hydrophilic cream based emollient like petrolatum 20% cetomacrogol cream as the basis for our topical

product. Possible irritants of inflamed skin, like alcohol, propylene glycol or urea should be avoided. Secondary skin infections with Pseudomonas aeruginosa appear to be rare, but may be linked to the treatment via the moist environment induced by the bandages. Insufficient cleaning of the water sprayers used to rewet the first layer of bandages may constitute a cause of infection and frequent cleaning of these sprayers is advised. Refractory skin lesions on areas not covered by bandages were sometimes seen if solitary arm and leg pieces of the bandages were not adequately attached to the central body piece. When using the Tubifast Garments® this problem does not occur.

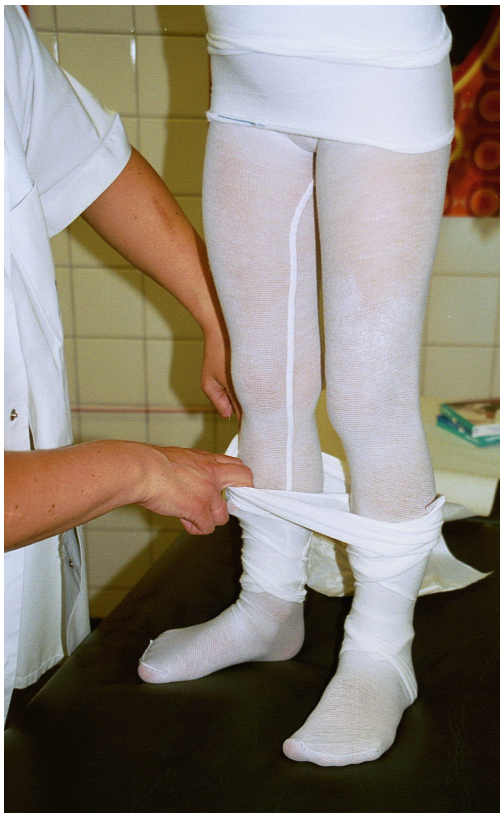

Figure 1
Application of the second layer of dry Tubifast Garments® on top of the first wetted layer

Whether or not there is an increased risk for other skin infections, such as a bacterial impetigo or eczema herpeticum, is still unclear. Both events are well known complications in children with AD. However, at the moment there is no data suggesting that they occur more frequently during WWT. If these or other secondary skin infections, such as mollusca contagiosa or viral warts, do occur during WWT the treatment should be (temporarily) stopped and if possible adequate treatment of the secondary skin infection started.

Although striae distensa have not been reported during a wet-wrap intervention treatment, they were observed by us during a long-term intermittent treatment in an adult.[12] Because children entering puberty are already at risk of developing striae, we advocate caution at this age and consider it to be a relative contraindication for WWT.

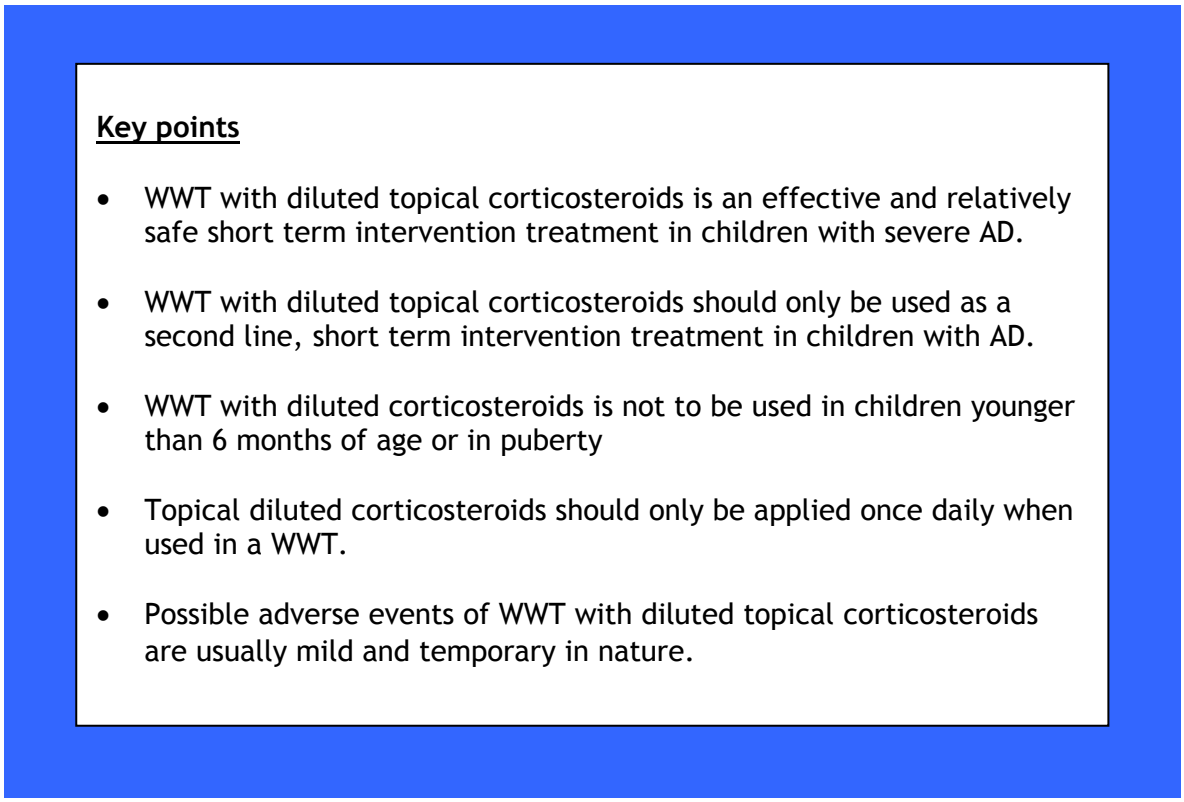

Figure 2
Key points to remember

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Chapter 6

General discussion and summary

General discussion

Summary

General discussion

Caring for children with severe and/or refractory atopic dermatitis (AD) remains challenging for both medical practitioners and caregivers. The diagnostic work-up as well as disease management differs markedly from that in patients with mild or moderate disease, although certain basic aspects remain the same. A desire to improve our daily clinical practice for these patients formed the basis for the studies outlined in this thesis.

The first study was aimed at improving our allergologic work-up in young children with AD by evaluating the use of the Atopy Patch Test (APT) with food allergens in patients aged 0-3 years. Next to our current diagnostic protocol for the diagnosis of a clinically relevant food allergy in this patient group, we found the additional value of the APT to be very limited at best. The results do not justify the time consuming nature of the skin test in our daily clinical practice and we currently advocate using it for research purposes only. In a second study we evaluated the characteristics of the APT with aeroallergens in the same patient population. We found a substantial number of clear-cut positive APT reactions with house dust mite, cat- and dog dander, with a relatively high percentage of urticarial reactions. As there is no gold standard for the diagnosis of a relevant allergy to aeroallergens in patients with AD, we did not attempt any conclusions with regard to the clinical relevance of these positive reactions. We believe further studies with the APT are worthwhile to undertake because it does function as an allergen specific delayed type hypersensitivity reaction, which still seems promising for future use as a diagnostic or prognostic test.

In the second part of this thesis we evaluated plasma matrix metalloproteinase (MMP)-9 as a possible objective laboratory marker for the assessment of disease severity in AD. Assessment of disease severity is essential in monitoring efficacy of therapeutic interventions, both in daily clinical practice as well as in clinical trails. Our results showed significantly increased levels of plasma MMP-9 in patients with AD compared to healthy controls, suggesting a role for MMP-9 in the pathogenesis of AD. However, disease specificity remains questionable and we could not find a significant correlation between plasma MMP-9 and the objective SCORAD or TIS as clinical markers of disease severity. Larger studies are needed to evaluate plasma MMP-9 levels in AD, including stratification for concomitant asthma and allergic rhinitis.

The publications on wet-wrap treatment (WWT) with diluted corticosteroids in the last section of this thesis substantiate the use of this treatment modality as an effective and relatively safe intervention treatment in young children with AD. However, caution is still warranted and we believe it should be reserved as a second line treatment in patients with severe or refractory skin disease. Long term treatment seems feasible, but adequate instruction and a careful follow-up are essential. Larger prospective studies are needed to further evaluate the efficacy and safety profile of WWT in AD. Next to standardized clinical efficacy and safety parameters, these studies should also include quality of life assessments and cost-benefit ratios as outcome parameters.

Summary

The general introduction in ***chapter 1*** provides an overview on atopic dermatitis (AD), as a relatively common inflammatory skin disease with a predominance in infancy and early childhood. The clinical care for patients with severe and/or refractory AD differs from that in patients with mild and moderate disease, especially with regards to diagnostic work-up and management. This forms the basis of this thesis, for which the aims are described in ***chapter 2***.

The studies in ***chapter 3*** are centred around the possible role of the Atopy Patch Test (APT) in the diagnostic work-up of paediatric patients with AD. The APT is a skin test aimed at detecting delayed type, eczematous reactions to food and aero-allergens commonly associated with direct type, IgE mediated reactions. The chapter starts of with an European multicenter study our research-group participated in. This study was initiated to define appropriate APT methodology, safety aspects and the relationship between the APT and the clinical history of eczema flares. It was added to this thesis with kind permission of first author Ulf Darsow. After the inclusion for this study was completed we continued with our own studies detailed in the other two publications in this chapter.

The first study was designed to evaluate the additional value of the APT within our own diagnostic protocol for the diagnosis of a relevant food allergy in children below the age of 3 years with AD. The results showed clinically relevant food allergies in 23% (egg white) to 28% (cow's milk and peanut) of our patient population. The additional value of the APT for reaching this diagnosis was not statistically significant for cow's milk and egg white, but was statistically significant for peanut. However, this statistically significant value does not exclude the need for oral challenges as there were false negative as well as false positive APT results.

The second study was aimed at evaluating the APT with aero-allergens in children with AD below the age of three years. The presence of positive APT reactions was investigated, including their correlation with serum specific IgE and/or the presence of positive skin prick tests (SPT). We found a substantial number of clear-cut positive APT reactions to house dust mite, cat- and dog dander in our pediatric patient population, with a relatively high percentage of urticarial reactions. There was a statistically significant agreement between the APT and serum specific IgE as well as the SPT, although the strength of agreement was only fair to moderate. As there is no gold standard for the diagnosis of a relevant allergy to aeroallergens in patients with AD, we did not attempt any conclusions with regard to the clinical relevance of the positive APT reactions.

The study described in ***chapter 4*** was initiated to evaluate the presence of plasma Matrix metalloproteinase (MMP)-9 in patients with AD as compared to healthy controls, including the possible correlation between plasma MMP-9 and disease severity. The MMP's form a group of enzymes, which are capable of hydrolysing protein structures in the extra-cellular matrix of tissues, thus playing a role in invasive tumour growth, tissue remodelling and infiltration of inflammatory cells in tissues. Through cleavage they also play a role in shedding of cell membrane associated proteins and activation of pro-enzymes, thus being integrated in the inter-cellular signalling pathways. Our results showed significantly increased levels of MMP-9 in plasma of patients with AD as compared to healthy controls, suggesting a role for MMP-9 in the pathogenesis of AD. However, we could not find a significant correlation between plasma MMP-9 levels and the objective SCORAD or Three Item Severity score (TIS), as markers of disease severity.

The publications in ***chapter 5*** were initiated to further substantiate and optimize wet-wrap treatment (WWT) with diluted topical corticosteroids as an intervention treatment for patients with severe and/or refractory AD. This treatment modality combines daily application of diluted topical corticosteroids with a moist first layer of cotton bandages, followed by a second dry layer.

The first publication in this chapter describes a retrospective study on the use of a standardized WWT protocol in patients with severe and/or refractory AD. Fourteen children and 12 adults were treated, using a left-right comparison between different dilutions of fluticason propionate 0,05% (FP) cream. After one week of once daily applications on the entire skin, a long term treatment was initiated, limiting the diluted corticosteroid to eczematous skin areas for only four consecutive days each week. The results showed that WWT with diluted corticosteroids, as described above, is a very effective intervention treatment. The most important side effect consisted of a (temporary) suppression of the HPA-axis in a minority of the patients. The use of a less potent dilution of FP cream diminishes this risk, while maintaining a good efficacy. Long-term treatment at home is feasible when patients (and parents) are motivated and provided with adequate instruction and guidance.

The second publication describes a critical review of the available literature on the WWT as an intervention treatment in children with severe and/or refractory AD. The different publications were evaluated using the guidelines from the National Health Service (NHS) Centre for Reviews and Dissemination of the University of York. Based on the available data we were able to formulate the following conclusions with a grade C of recommendation.

1. WWT using cream or ointment and a double layer of cotton bandages with a moist first layer and a dry second layer, is an efficacious short-term intervention treatment in children with severe and/or refractory AD.
2. The use of wet-wrap dressings with diluted topical corticosteroids is a more efficacious short-term intervention treatment in children with severe and/or refractory AD than wet-wrap dressings with emollients only.
3. The use of wet-wrap dressings with diluted topical corticosteroids for up to 14 days is a safe intervention treatment in children with severe and/or refractory AD, with temporary systemic bioactivity of the corticosteroids as the only reported serious side effect.
4. Lowering the absolute amount of applied topical corticosteroid to once daily application and further dilution of the product can reduce the risk of systemic bioactivity.

The third publication reflects the combined knowledge of a panel of experts on the treatment of patients with AD using wet-wrap dressings with diluted corticosteroids and/or emollients. They met on four separate occasions, sharing their experiences on the methodology, (contra-)indications, efficacy and safety. The conclusions they reached were that WWT using diluted corticosteroids is a relatively safe addition to the therapeutic treatment options for children and adults with severe and/or refractory AD. Instruction is extremely important and WWT should only be employed by practitioners trained in its use. Specialized nursing care is essential, especially when using WWT for prolonged periods.

The goal of the fourth publication was to provide a guideline as a starting point for clinicians who are interested in using WWT in their own clinical practice. Several practical issues surrounding the use of WWT are addressed by describing our own experiences supplemented with data from the literature.

Chapter 7

The wind up

Acknowledgements (Dutch)
(Nederlandstalig dankwoord)

Curriculum vitae (Dutch)
(Nederlandstalig curriculum vitae)

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Als het einde van een promotietraject begint te naderen ga je vanzelf nadenken over het schrijven van een dankwoord voor alle mensen die direct of indirect een bijdrage hebben geleverd aan het tot stand komen van het boekje. Uiteindelijk zijn dat er nogal wat en is het haast ondoenlijk om ze hier allemaal te noemen. Toch volgt hieronder een poging met bij voorbaat mijn excuses aan diegenen die ik vergeten ben. Ook jullie bijdrage werd zonder meer gewaardeerd.

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Curriculum vitae

De schrijver van dit proefschrift werd op 18 april 1974 geboren in Roosendaal. Het gezin verhuisde kort na zijn geboorte naar Oud-Beijerland, waar hij in 1992 zijn VWO eindexamen behaalde aan de plaatselijke Regionale Scholengemeenschap. Hierna volgde de studie Geneeskunde aan de Erasmus Universiteit te Rotterdam, waar hij in 1996 zijn doctoraal examen behaalde. Zijn afstudeeronderzoek vond plaats op de polikliniek kinderdermatologie van het Erasmus MC - Sophia Kinderziekenhuis en was getiteld "congenitale hypotrichosen". Na het doorlopen van de verschillende co-schappen behaalde hij in 1999 zijn artsexamen, waarna hij als onderzoeksarts ging werken op de afdeling Dermatologie en Venereologie van het Erasmus MC. In 2001 begon hij hier aan de opleiding tot dermatoloog welke hij in mei 2005 volbracht. Sindsdien is hij als dermatoloog werkzaam in het Maasstad Ziekenhuis te Rotterdam, met als aandachtsgebied de kinderdermatologie. Als vakgerelateerde nevenfuncties is hij momenteel werkzaam als bestuurslid van de Vereniging voor Kinderdermatologie, secretaris van het organiserend comité van de jaarlijkse cursus "Diagnostiek en Therapie in de Kinderdermatologie" en lid van de domeingroep "Eczeem en Allergie" van de Nederlandse Vereniging voor Dermatologie en Venereologie.

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