Development of new treatment modalities for atopic dermatitis
van Leent, E.J.M.

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Chapter 1A

Introduction to Atopic Dermatitis

E.J.M. Van Leent and J.D. Bos

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Chapter 1A

INTRODUCTION

Definition and epidemiology
Atopic dermatitis is a chronic, itching skin disease with a relapsing course. It forms part of the atopic syndrome, also known as atopy. Other clinical manifestations of atopy are allergic rhinitis (hay fever), allergic (extrinsic) asthma, certain gastrointestinal allergies, and allergic conjunctivitis. Associated disorders include anaphylaxis, urticaria, and dyshidrotic eczema, as well as a variety of other symptoms and signs known as the minor criteria of Hanifin and Rajka.

Clinical and laboratory criteria have been developed for the definition of atopic dermatitis. The most widely used are those of Hanifin & Rajka (1980) (Table 1). Recently, the millennium criteria for the diagnosis of atopic eczema were defined (Bos et al 1998) (Table 2). In the millenium criteria, emphasis is given to the presence of allergen-specific IgE in the patient. When present, the patient has truly atopic eczema (also known as extrinsic atopic eczema) and recommendation of allergen avoidance makes sense. When allergen-specific IgE cannot be detected, the diagnosis of intrinsic atopic dermatitis is sometimes used, but we prefer to designate such patients as having atopiform dermatitis. They have no atopy and allergen avoidance does not make sense.

It is to be predicted that in the future, when a more precise knowledge of the multigenic background of atopy and atopic dermatitis has surfaced, genetic criteria will replace both immunological and clinical criteria (Forrest et al 1999). Atopic dermatitis is one of the most common skin diseases with a lifetime prevalence of up to 30%. Its incidence is increasing in Western countries (Williams 1992, Kay et al 1994). The highest incidence is among children.

Etiology and pathophysiology (Bos et al 1994)
Atopic dermatitis is a common disease entity forming part of a syndrome called atopy. A major immunological abnormality is the skewing, within the secondary immune organs (lymphoid tissues) of ThO cells towards Th2 lymphocytes, upon allergenic challenge. As a result, Th2 cells dominate the central responses, and through their specific cytokine secretion profile, induce B cells to produce allergen-specific IgE. These molecules are secreted into the circulation and will then sensitize different organs, by binding via FcεR receptors on mast cells and dendritic cells (including Langerhans cells). Allergenic challenge of a particular organ then leads to local allergic responses such as atopic dermatitis.

Within involved skin, a complex interplay between Th1 cells, Th2 cells, dendritic cells and mast cells leads to inflammation, and atopic allergens are
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Table 1  Diagnostic features of atopic dermatitis as defined by Hanifin & Rajka (Hanifin et al 1980)

Major features (3 of 4 present)
- pruritus
- typical morphology and distribution of skin lesions
- chronic or chronically relapsing dermatitis
- personal or family history of atopy

Minor features (3 of 23 present)
- xerosis
- ichthyosis / palmar hyperlinearity / keratosis pilaris
- immediate (type I) skin test reactivity
- elevated serum IgE
- early age of onset
- tendency towards cutaneous infections / impaired cell-mediated immunity
- tendency towards non-specific hand or foot dermatitis
- nipple eczema
- cheilitis
- recurrent conjunctivitis
- Dennie-Morgan infraorbital fold
- keratoconus
- anterior subcapsular cataracts
- orbital darkening
- facial pallor / erythema
- pityriasis alba
- anterior neck folds
- itch when sweating
- intolerance to wool and lipid solvents
- perifollicular accentuation
- food intolerance
- course influenced by environmental / emotional factors
- white dermographism / delayed blanch
Table 2  The millenium criteria for the diagnosis of atopic dermatitis (Bos et al 1998)

-1- mandatory criterium
  - presence of allergen-specific IgE:
    - historical, actual, or expected (in very young children)
    - in peripheral blood (RAST, ELISA) or in skin (intracutaneous challenge)

-2- principal criteria (2 of 3 present)
  - typical distribution and morphology of eczema lesions: infant, childhood, or adult type
    - if distribution is not typical, exclude other entity (dyshidrotic eczema, contact dermatitis, contact urticaria)
  - pruritus
  - chronic or chronically relapsing course

thought to play a role. Dendritic cells facilitate antigen processing (antigen focussing), by trapping of allergens through FcεRI receptor bound IgE. A major question open for research is whether this induction of immune responses and inflammation is indeed by nanoquantities of allergens present in skin, or that there is cross-reactivity with endogenous autoantigens that share epitope specificity with atopic allergens. It is clear that allergic reactions in particular to aeroallergens may play a role in the pathogenesis of the disease. On the other hand there are exogenous triggering factors like irritants, stress, pollutants and foods.

The atopy syndrome thus may be seen as a Th2 disease, while atopic dermatitis may be seen as the resulting IgE-mediated skin disorder. However, there are a number of patients (10% in some studies), who have atopic dermatitis clinically (and fulfilling the Hanifin & Rajka criteria), but allergen-specific IgE cannot be demonstrated in them. Some investigators therefore assume that IgE is not central in atopic dermatitis immunopathogenesis. In these allergen-specific IgE negative patients, there is atopy-specific Th2 polarization, but the Th2 cells do not produce sufficient amounts of IL-4 and/or IL-13, cytokines responsible for the IgM - IgE shift in B cells, although they do produce IL-5 and do not produce IFN-gamma, making them Th2 cells of a special subset (Akdis et al 1999).

Another explanation for the lack of discernable allergen-specific IgE in a limited subset of patients might be that we do not know the allergens in these patients that are responsible for the disease. Thus, there is no substrate for further testing and detecting allergen-specific IgE. Finally, it may be that these
patients have no atopy et al, and have a disease clinically similar to atopic dermatitis. Analogous to psoriasis and psoriasiform dermatitis, one might diagnose these patients as having atopiform dermatitis, as stated above.

**Clinical characteristics and course**
Atopic dermatitis is an itching, inflammatory skin disorder which usually starts in early childhood. The infant phase usually starts during the third month and is characterized by dry red scaling areas on the cheeks and chin, sparing the perioral and paranasal region. More severe cases show generalized papulation, redness, scaling and vesicles and crustae. The diaper area is usually spared. Exudative lesions typical of the infant phase are not as common in the childhood phase. The childhood phase is characterized by inflammation in flexural areas with depigmentation and the first signs of lichenification. The intense itch initiates the itch-scratch cycle. Marks of the adult phase are flexural inflammation, hand and/or foot dermatitis, inflammation around the eyes and lichenification of the anogenital area.

The dermatitis improves in most children. At the age of 18 months 50% of the patients have their disease completely resolved. Unfavorable prognostic factors are persistent dry or itchy skin, widespread dermatitis, associated allergic rhinitis, family history of atopic dermatitis, asthma, early age of onset and female sex. Most patients are in remission by the age of 30. In a few patients the disease becomes a lifelong chronic disease with periods of exacerbation and remission often related to the seasons.

**Diagnosis**
There are no laboratory tests available to confirm the diagnosis. Thus, the diagnosis is made clinically, for which diagnostic features have been described above.

The presence of atopic syndrome can be confirmed by serum testing (i.e. RAST) or by intracutaneous challenge, looking for allergen specific IgE antibodies to house dust, house dust mite, pollen (tree/grass/weed), animal dander (cat/dog), and molds. If atopy is not confirmed (in up to 10% of the patients with the clinical diagnosis according to the criteria of Hanifin and Rajka) by this test (or by the use of a skin prick test) the test should be repeated at a later point in time. This is especially applicable in small children.

**Differential diagnosis**
Table 3 gives an overview of differentiating features in other skin diseases.
Table 3: overview of differentiating features in other skin diseases
(modified from V.S. Beltrani)

<table>
<thead>
<tr>
<th>type of disease</th>
<th>diagnosis</th>
<th>differentiating features</th>
</tr>
</thead>
<tbody>
<tr>
<td>inflammatory</td>
<td>seborrhoeic eczema</td>
<td>seborrhoeic areas, no excoriated lesions on the extremities</td>
</tr>
<tr>
<td></td>
<td>nummular eczema</td>
<td>disseminated, coin-shaped, sharply demarcated</td>
</tr>
<tr>
<td></td>
<td>contact dermatitis</td>
<td>no improvement with appropriate treatment</td>
</tr>
<tr>
<td></td>
<td>photocontact- and</td>
<td>photo-distribution</td>
</tr>
<tr>
<td></td>
<td>photoallergic dermatitis</td>
<td></td>
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<tr>
<td></td>
<td>lichen simplex chronicus</td>
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<tr>
<td></td>
<td>psoriasis</td>
<td></td>
</tr>
<tr>
<td>infectious</td>
<td>dermatomycosis</td>
<td>KOH examination</td>
</tr>
<tr>
<td></td>
<td>scabies</td>
<td>interdigital or genital burrow, search for a mite</td>
</tr>
<tr>
<td></td>
<td>HIV-associated dermatoses</td>
<td>immunosuppression</td>
</tr>
<tr>
<td>immunologic</td>
<td>Wiskott-Aldrich syndrome</td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td>or infiltrative</td>
<td>hyper- IgE syndrome</td>
<td>recurrent bacterial infections</td>
</tr>
<tr>
<td></td>
<td>hypogammaglobulinemia</td>
<td>boys, lab gammaglobuline</td>
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<tr>
<td></td>
<td>Bruton’s type X-linked</td>
<td>purpura, telangectasia, fine sparse hairs</td>
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<tr>
<td></td>
<td>agammaglobulinemia</td>
<td>pyoderma, candidiasis, present from birth</td>
</tr>
<tr>
<td></td>
<td>severe combined</td>
<td>clinical presentation</td>
</tr>
<tr>
<td></td>
<td>immunodeficiency (SCID)</td>
<td>fever, weight loss, lymphadenopathy</td>
</tr>
<tr>
<td></td>
<td>cutaneous T-cell lymphoma</td>
<td>(CTCL)</td>
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<tr>
<td></td>
<td>cutaneous lymphomas</td>
<td></td>
</tr>
<tr>
<td>genetic</td>
<td>ectodermal dysplasia</td>
<td>anhidrosis, dental or hair abnormalities</td>
</tr>
<tr>
<td></td>
<td>Netherton’s syndrome</td>
<td>bamboo hairs</td>
</tr>
<tr>
<td></td>
<td>phenylketonuria</td>
<td>pyogenic infections, lab phenylalanine</td>
</tr>
<tr>
<td></td>
<td>ataxia telangiectasia</td>
<td>ataxia, telangiectasia, pigmentation abnormalities</td>
</tr>
<tr>
<td></td>
<td>Hurler’s syndrome</td>
<td>ivory-white nodules or ridges</td>
</tr>
</tbody>
</table>
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TREATMENT

1. General therapeutic guidelines (Przybilla et al 1994)

1.a Elimination of triggering factors
The most important aeroallergens in atopy are house dust, house dust mite, pollen (tree/grass/weed), animal dander (cat/dog), and molds. It is generally believed that they should be avoided. In fact for house dust mite allergens, elimination has indeed been proved to have a beneficial effect on the course of atopic dermatitis. Contact with these allergens is prevented by using dust-mite proof (goretex) covers for mattresses and pillows, wet-mopping floors and avoiding rugs (especially in bedrooms).

Several investigators emphasize the etiologic role of food allergens in atopic dermatitis and note improvement after an elimination diet. Common food allergens implicated in atopic dermatitis are: milk, egg whites, peanuts, soybeans, tree nuts, fish, shellfish and wheat. It is accepted that with increasing age, the importance of food allergens rapidly decreases. The frequency of positive reactions to aeroallergens increases with age whereas the frequency of positive reactions to food allergens decreases with age.

Irritants like wool, soaps, perfumes, makeup, prolonged hot showers, high temperature, low humidity can all contribute to the severity of atopic dermatitis and should be avoided. Stress; anxiety can be a triggering factor, as well as depression, because it may reduce the threshold for pruritus. To reduce the scratch behavior the help of a psychologist can be useful.

1.b Indifferent therapies
Emollients for preserving and restoring the stratum corneum barrier should be used together with other topical treatments, and are to be continued long after topical corticosteroids have been stopped. Only in case of impetiginization are emollients contra-indicated. Petroleum jelly is very effective. For practical reasons we recommend a combination of white petrolatum with liquid paraffine in equal parts. They are to be prescribed in large amounts. When the occlusive effect is to pronounced, emollients can cause folliculitis. This is a good reason to reduce the amount of grease in the emollient and replace it for 10 to 50% cream. Immediate lubrication after a bath is very effective. Bath-oils can be used for that, also when a shower is used.

1.c Topical antimicrobals
Ketoconazole shampoo and topical miconazol do not enhance the improvement of conventional therapy, compared to placebo. To decrease the bacterial load of the skin, chloorhexidin or iodide solutions can be used topically. This is
recommended for patients with recurrent bacterial infection of the skin. In general, many clinicians assume that exacerbations of atopic dermatitis are the result of bacterial superinfections, mainly due to *Staphylococcus aureus*. Thus, fucidin has become a standard in many countries. With this topical antibiotic, that can be combined with corticosteroids, the bacterial load is brought down and secondary infection and impetiginisation are minimized. Another approach is by adding antiseptics to the bathing water in mineral bathing oils. Benzalkonium chloride is used for that purpose.

1.d  *Diets* (Atherton 1988)
The role of diets and food allergy/intolerance in the management of atopic dermatitis is controversial. For pregnant or nursing women at risk, a hypoallergenic diet can reduce the prevalence of atopic dermatitis in their high-risk infants. The use of diets in such a situation may decrease the incidence of allergic diseases from 40% to 14%. Hypoallergenic diets are also recommendable for children in their first months to years. Because sensitivity to food tends to wane with age, consideration can be given to reintroducing eliminated foods to the diet, with the exception of peanuts. For the hypoallergenetic diet, elimination of milk and egg whites and to a less extend peanuts, soybeans, tree nuts, fish, shellfish and wheat are often recommended.

1.e  *Treatment failure*
Reasons for failure to respond to adequate therapy are: poor patient compliance, allergic contact dermatitis to a topical medicine or vehiculum, the simultaneous occurrence of asthma or hay fever, inadequate sedation and continued emotional stress.

2. **Recommended therapies**

2.a  *Topical therapies*
Before corticosteroids were introduced in the late fifty's of the previous century, coal tar ointment was the most frequently used therapy. Tar is effective but not working quickly. Nowadays coal tar preparations are used to save topical corticosteroids for the times the dermatitis is exacerbating. Besides cosmetic distress tar can enhance the appearance of sunburn. Tar shampoos are often beneficial for scalp involvement.

Topical antihistamines and non-steroidal anti-inflammatory drugs (NSAID's) such as doxepin, sodium cromoglycate, bisacodyl or bufexamac, are not recommended because they do not work topically (NSAID's) or they tend to sensitize and result in allergic contact dermatitis (topical antihistamines).
A large variety of topical steroids is available (Goerz et al. 1991). The potency of these corticosteroids ranges from mild to very potent. In addition, the vehiculum may differ, which is of limited influence on therapeutic efficacy. Most steroid preparations are available as lotion, cream, fatty-cream and ointment. In special cases it is possible to choose different ointments and/or creams as a base for the steroid, if the pharmacist is willing to cooperate. This is very helpful in case of an allergy to ingredients of the vehiculum.

There are different grading systems for the potency of the steroids. Some authors use group 1 for the most potent, to group 6 for the least potent preparations, while others are using a grade definition with grade 1 steroids for the least potent and grade 4 steroids for the most potent preparations. An overview is given in table 4.

\textit{table 4} \textit{representative topical corticosteroids}

\textbf{mild}
hydrocortisone acetate

\textbf{moderate potent}
alclometasone dipropionate
clobetasol butyrate
fluocinolone acetonide
fluocortin butylester
flumetason pivalate
triamcinolon acetonide

\textbf{potent}
amcinonide
betamethasone valerate/dipropionate/benzoate
budesonide
desoximethasone
diflucortolone valerate
fluocinonide
fluticasone

\textbf{very potent}
beclomethasone dipropionate
clobetasol propionate

To prevent tachyphylaxis, side effects, and rebound phenomena, it is better to use a potent steroid intermittent or for a short term, followed by a less potent
preparation or the alternate use with emollients. It is recommended to use topical steroids once daily in combination with at least once daily application of emollients. In the first weeks corticosteroids are to be used every day; after the acute phase an alternate use is recommended. In this pulse-therapy the topical steroid is used for four to five consecutive days a week, while during the other two to three days only emollients, or tar preparations, are recommended. The patient should be instructed not to stop the treatment too early, a few days up to one week after the redness of the skin has disappeared will be sufficient.

Wet wraps are used for short periods during acute exacerbations. They can be used as occlusion after topical therapy, to enhance the absorption. It is also protective to persistent scratching, and decreases the itch by cooling of the skin.

In children, extra precautions are to be considered when using topical corticosteroids. Growth retardation is a major issue and in severe cases where long periods of corticosteroid application is necessary, keeping growth curves should be part of the patient follow up.

2.b Systemic therapies
Antihistamines are used to reduce the self-inflicted damage to the involved skin. The relief of itching may be little, the sedating/calming effect can give a more comfortable sleep. Therefore, the sedating antihistamines are more effective in comparison to newer non-sedating antihistamines. Sedating antihistamines should be avoided in young children under 1 year of age. In pregnancy, it is said that promethazine is safe.

Antibiotics are also of benefit when there is no clear impetiginization, probably by reducing the bacterial load of the skin. It is recommended to start with clarithromycin 2dd 250mg or erythromycin 4dd 250-500mg for one week (or equivalent doses in children: erythromycin 50 mg/kg/day, clarithromycin 7.5 mg/kg/day). If necessary this can be continued for some weeks, if desired half of the dose can be tried.

Systemic use of cyclosporin (CsA) has been proven to be effective but its use is restricted to severe cases only (Snowden et al 1991). After double checking the serum creatinine a starting dose of 3mg/kg/day is advised, and a maximum of 5 mg/kg/day should be adhered to. After control is achieved, the dose should be slowly reduced. Controls of blood pressure and serum creatinine must be performed at a regular (6-weekly) intervals. Trough levels can be measured, for example in cases where a response is expected but not apparent.

The use of a short course of oral prednisolone, for example in a dose of 2dd 20mg (adult dose), is occasionally needed to control difficult cases. The main problem with short courses is the rebound effect, shortly after the medication is discontinued. Other disadvantages are the loss of the patient compliance
towards topical steroids and the association with the development of atopic cataracts.

2.c Phototherapy and photo-chemotherapy (Krutmann et al 1992)
Many patients are convinced of the benefit of exposure to sunlight. This has resulted in the development of different UV schedules for the management of this inflammatory skin disease. In addition to UVA, PUVA, UVA+UVB, and UVB, UVA1 (wavelength 340-400nm) has been recently developed as a promising alternative for atopic dermatitis.

Studies have indicated that UVB radiation (295-315nm) is not suitable for acute exacerbations and is thus restricted to chronic cases. Combinations of UVB with UVA (300-400nm) are more effective than UVB alone and the result can be improved by increasing the UVA portion. Systemic photo-chemotherapy, PUVA, is more effective but is associated with a number of side effects such as the rebound-effect and an increased risk of developing skin cancer.

2.d Hospitalization and day-care centers
Patients with severe, generalized inflammation who do not respond to or flare soon after the use of topical steroids or appear erythrodermic are candidates for hospitalization. By hospitalization the patient is protected from allergens and stressors. There is an almost guaranteed compliance, and education can be more effective. Time consuming or difficult treatments can be done, and different therapies can be combined. The admission period can also be used for identifying potential allergens correctly.

2.e Treatment of complications
Bacterial infections:
• Impetiginization. Because of the high rate of colonization with *Staphylococcus aureus* in patients with atopic dermatitis, infection of the skin is frequent in these patients. Even a good treatment cannot prevent recolonization when the dermatitis is in remission.
• Superantigens. The bacterial load of the skin also gives rise to superantigen exposure which is associated with worsening of the dermatitis. Superantigens themselves are difficult to believe to be directly responsible in view of their molecular weight, but it may be that they are rubbed into the epidermis by scratching. For the treatment there are topical cleansing products with chlorhexidin or iodine. Topical antibiotics such as 2% mupirocine ointment or 2% sodium fusidate ointment may also be considered. Impetiginization can be treated well with systemic antibiotics. It is preferable to choose the antibiotic knowing the results of a bacterial
sensitivity test. For a blinded start, one week clarithromycin 2 dd 250 mg or erythromycin 4 dd 250-500 mg (adult doses) are recommended. In case of known allergy or insensitivity to these macrolides, one week flucloxacilline 3dd 500mg or azitromycine 2dd 250mg (adult doses) are recommended.

Viral infections:

- Eczema herpeticum (Kaposi’s varicelliform eruption). Patients with atopic dermatitis are susceptible to the spread of cutaneous (not systemic) Herpes simplex infection. The spread of Herpes simplex is enhanced by the damaged stratum corneum barrier. Typical for atopic dermatitis is the spread from a small area to a more extensive area or to an area elsewhere on the body. Especially in the first 48 hours an anti-viral treatment such as valacyclovir 3dd 100mg for 7 days, or acyclovir 5dd 800mg for 5 days can be useful. For severe cases (i.e. fever), hospitalization for intra-venous treatment with aciclovir 5mg/kg every 8 hours for 5 days is to be considered. In case of neuralgia analgesics such as paracetamol 500mg or paracetamol-codeine 500/20mg up to 6 times a day (maximum adult dose) can give relief.

- Warts and molluscum contagiosum: Patients with atopic dermatitis who contract warts are relatively recalcitrant to treatment, but their treatment does not differ from those in non-atopics.

Dermatophycosis:

In particular Trichophyton rubrum can be treated with antifungal agents, but creams like ketoconazole can be drying and irritating.

Cheiro/podo pompholyx:

In the acute phase the hands and/or feet should be soaked three or four times a day in Burow’s solution (aluminium acetate 10%) or zinc sulphate ointment may be applied. The soaks can be stopped after a few days, when the eruption subsides. A zinc cream or oily calamine lotion can be substituted, in the chronic phase topical steroids are useful. In case of secondary bacterial infection flucloxacillin (adult dose 3dd 500mg) can be used.
3. Alternative and experimental treatments

3.a Experimental therapies

Essential fatty acids have been found in increased levels in lesional skin of atopic dermatitis patients, with normal values in unlesional skin. In addition abnormalities in the fatty acid composition in breast milk of mothers with affected children have been found. It has been suggested that a deficiency of these fatty acids plays a role in the pathogenesis of atopic dermatitis. Dietary supplementation with evening primrose oil and marine fish oil did not demonstrate any significant clinical improvement in double-blind, placebo-controlled trials.

Chinese herbs have nonsteroidal anti-inflammatory activities, some of them have in addition also steroid like-, antihistaminic- or immunosuppressive activity. The herbal therapy seems to target the inflammatory character of the disease. Positive results have been reported, but its potential hepatotoxicity has to be studied. Other problems are a guaranteed constant quality and the unpalatability of this therapy.

Because airborne allergens such as Dermatophagoides pteronyssinus seem to play an important role in atopic dermatitis as a triggering factor, allergen desensitization with extracts of these allergens have been published. Some investigators reported positive results in unblinded uncontrolled studies while others reported no alleviation after desensitization in a placebo-controlled, double-blind study. The major limitation of this treatment is the complicated procedure of preparing specific immune complexes.

Atopic patients have a reduced interferon-gamma (IFN-γ) production, leading to an overproduction of IgE. This suggest that IFN-γ may be effective in the treatment of atopic dermatitis. Subcutaneous injection of IFN-γ is effective in nearly half of the patients, achieving 50% improvement. A major disadvantage in is its price.

Thymic factors have been tried in atopic dermatitis. Intramuscular thymostimulin (TP-1) achieved no significant difference to placebo, subcutaneous thymopentin (TP-5) achieved a small improvement in combination with topical steroids and oral antihistamines.

Patients with atopic dermatitis are predisposed to cutaneous infections, often with Staphylococcus aureus. This is a well known triggering factor. Topical gamma globulin (IgG) preparations have been used with specific antimicrobial antibodies with neutralizing and opsonizing activity. Improvement was reported, but double-blind placebo-controlled studies are not available.

In atopic dermatitis patients phosphodiesterase activity in mononuclear leukocytes has been reported to be increased. Phosphodiesterase inhibitors are
used experimentally as therapy in atopic dermatitis. However these agents are not yet clinically available.

3.2 Imminent new therapies
Tacrolimus (FK 506) and pimecrolimus (SDZ ASM 981) are new macrolide-type inflammatory cytokine inhibitors, with a mechanism of action similar to cyclosporin (Nakagawa et al 1994, Ruzicka et al 1997, Van Leent et al 1998). In contrast to cyclosporin A, they are effective in the topical treatment of atopic dermatitis, due to their relatively small size (Bos & Meinard 2000). Both compounds are highly effective against itch, one of the most prominent problems of patients with atopic dermatitis. In contrast to topical corticosteroids, these compounds seems to have a more favorable side-effect profile. This might be of importance for patients suffering from the local side effects of corticosteroids such as atrophy, telangiectasia, striae or tachyphylaxis, or systemic side effects such as adrenal suppression. Burning of the skin or a feeling of warmth is a frequently reported side-effect of these new compounds. This is only a minor problem, disappearing after a few days. These topical inflammatory cytokine inhibitors are, similar to corticosteroids, contra-indicated for use in infected skin.

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