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Clinical pearls from atopic dermatitis and its infectious complications

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Summary

Atopic dermatitis (AD) is clinically very heterogeneous and these differences can cause confusion. Differential diagnosis is also complicated by co-infections, particularly in infancy and early childhood. This paper describes the stages and differential diagnosis during the various stages of childhood. The authors also provide advice on how to distinguish between AD and other disorders together with guidance on tackling common issues with treatment such as steroid phobia.

Atopic dermatitis (AD) is clinically very heterogeneous and varies with ethnicity¹⁻³ and age.^{4,5} The diagnosis of AD can be confusing but primarily depends on the criteria put forward by Hanifin and Rajka.⁶ Although AD is varied in its manifestations, there are a number of typical clinical features. Due to the defective cellular immunity and a defective epidermal barrier in AD, it is frequently complicated by infections. Infections themselves usually exacerbate the symptoms of AD, making the proper treatment or control of these infections very important.

Recent developments

Typical clinical features according to age

During infancy (2 months – 2 years)

The eczematous lesions typically start around the perioral area, where saliva and/or food often irritate the skin, usually after 2 months of age (Fig. 1). Sometimes these lesions are noticed around the periorbital area, where the tears can cause skin irritation and lead to frequent rubbing with the hands. However, there is a tendency for sparing of the nasolabial folds and vermillion borders, even when the eczema becomes severe enough to involve the whole face. This is apparently due to these areas being rich in sebaceous glands and difficult to scratch with the fingers. The skin lesions also spread down to the trunk and extremities with dry, scaly pruritic patches commonly developing on these regions. The extensor surfaces of the extremities are regularly affected during infancy.⁷

Quite frequently there are fine scaly lesions with or without erythema on the scalp; the so-called 'scalp scaling'.^{4,8,9} When the scaling is very severe with a thick yellowish crust, it is called 'cradle cap'. Scalp scaling can be a manifestation of AD, seborrhoeic dermatitis (SD) or another condition. When scalp scaling develops during infancy, usually after 2 months of age, it is a manifestation of AD. However, if it is seen before 2 months of age or after puberty, it is more likely to be a symptom of SD. This is because SD is a disease of the seborrhoeic area and sebaceous gland activity is high during the neonatal period, decreases after this time, and then becomes very high after puberty.¹⁰

Periauricular skin is also commonly affected by AD in the form of infra-auricular fissures or nonspecific eczematous skin lesions. Because periauricular areas usually display some eczematous lesions, periauricular eczematization (Fig. 2) is the more preferred term.^{11,12}

Childhood (2–10 years)

Flexural areas typically become affected during this stage (Fig. 3). There are no obvious answers as to why flexural areas are involved,^{13,14} but these are sites where more sweating and greater friction between skin folds occurs. The antecubital fossae, wrists (both the dorsal and ventral sides), popliteal fossae, neck and infragluteal folds are all typically involved.³ Flexural areas of the neck frequently show eczema (the so-called ‘anterior neck folds’).

These areas also display generalized dry skin, which is commonly associated with ichthyosis, hyperlinear palms and keratosis pilaris (sometimes called the ‘ichthyosis triad’).¹⁵ In addition, the skin of the trunk can feel very coarse with perifollicular accentuation due to dryness. Cheilitis, especially of the upper lip, is another common symptom. The periorbital areas are regularly involved due to frequent rubbing with the hands leading to eyelid eczema⁵ and periorbital pigmentation.

Nonspecific hand/foot dermatitis is commonly observed and both the dorsal and ventral sides of the hands and feet can be affected. On the soles of the feet, this takes the form of forefoot eczema and/or heel eczema, while the arch of the sole is often spared.

Adolescents over 12 years and adults

The chronic nature of AD leads to more pronounced thickening or lichenification, not only of the flexural areas, but also of the forehead and other areas. Sometimes reticulate pigmentation of the neck or ‘dirty neck’¹⁶ is observed. Nipple eczema^{3,5} is a common symptom at this stage (Fig. 4), especially in girls.¹⁷ During the adolescent or adult stage, facial symptoms are usually aggravated and patients can sometimes display what is called ‘atopic red face’.^{16,18}

Clinical pearls

- AD lesions typically start on the face, especially around the mouth, where saliva and moist food irritate the skin.
- Scalp scaling and periauricular eczematization are common symptoms. The periorbital area is often affected and shows periorbital pigmentation.
- Extensor surfaces of the extremities are commonly affected, initially during infancy, followed by flexural involvements during childhood.
- Nonspecific hand/food dermatitis and nipple eczema are common.

Steroid phobia

Quite often, young mothers will visit the outpatient clinic with very young infants who have severe AD lesions, but say that they have never used ‘very bad’ topical corticosteroids (TCS) on their babies. This is usually due to misconceptions about TCS. Many parents or patients themselves have false steroid phobia and are reluctant to use TCS.^{19–21} Without proper treatment with TCS, eczema becomes aggravated and needs more aggressive treatment. Only 1–2 weeks after the application of TCS, skin lesions become much improved, with the vicious

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cycle broken, meaning that improvement can thereafter be maintained by intermittent or minimal use of TCS along with optimal skin care.

Clinical pearls

- The most effective way to suppress the skin inflammation caused by AD is to apply TCS to the lesions. Patient education about the proper use of TCS is of the utmost importance if the vicious cycle of AD is to be broken.

Topical calcineurin inhibitors

One of the real breakthroughs in the treatment of AD has been the introduction of topical calcineurin inhibitors (TCIs). The efficacy and safety of TCIs, especially for face and neck lesions, has already been confirmed in both Western^{22–24} and Asian studies.²⁵

Both tacrolimus (Protopic®) and pimecrolimus (Elidel®) are effectively used to treat facial lesions, especially around the eyes. The clinical efficacy of these medications can be observed within 2 weeks. These days, proactive therapy with tacrolimus ointment is the preferred option for effective maintenance therapy.²⁶

TCIs have been prescribed for children less than 2 years old (although this is off-label use) in cases where continuous and prolonged application of TCS would be necessary to treat the facial lesions. Theoretically, the use of TCIs in pregnant women should be safe with regard to teratogenicity and fetal or maternal complication,^{27–29} and considering systemic exposure to this drug. However, there have been no studies of TCIs during pregnancy.

The long-term safety of TCIs has already been proven in numerous clinical trials. Clinical data show no evidence of increased risk of malignancies with TCIs.^{30–32}

Cases with severe atopic dermatitis necessitating the use of immunosuppressants or immune modulators

When the symptoms of AD, especially in children, are too severe for patients to lead a normal daily life and cannot be controlled by conventional treatments, immunosuppressants may be prescribed. Of course, there are different options, but the following drugs can be used very effectively and safely.

Ciclosporin

Ciclosporin is the drug of choice for patients with AD that is refractory to conventional treatments. Many studies have been carried out to date, showing the optimal starting dose of ciclosporin (3–5 mg kg⁻¹ daily); how the dose should be tapered down; and how long the drug can be given to a patient, using a monitoring schedule for possible adverse events.^{33–35}

This drug is also effective in childhood AD, maybe more so than for adults with the condition. When the AD symptoms are so severe in children that they cannot be controlled by conventional therapies, a short course (approximately 3 months) of ciclosporin can suppress

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disease activity sufficiently, and thereafter, the patient's AD can be managed with conventional care.

Methotrexate

Although there are currently no controlled studies of methotrexate (MTX) for the treatment of AD, MTX is effective in some cases that are resistant to ciclosporin.^{36,37} The dosing schedule is usually three times every 12 h for a week. This schedule is very convenient for the patient. Compliance therefore tends to be very good, although it takes about 2–4 weeks for the true efficacy of MTX to be seen.

Intravenous immunoglobulin

Although there are conflicting reports about its efficacy, intravenous immunoglobulin (IVIG), at 2 g kg⁻¹ monthly (generally given as a dose of 0.5 g kg⁻¹ every day for 4 days) for a minimum of 3 months, is worth trying in children.^{38,39} Sometimes children with very severe AD who do not respond to ciclosporin or other immunosuppressants show significant improvement with this 3-month schedule.

Clinical pearls

- When patients' symptoms of AD are so severe that they cannot be treated by conventional therapies, immunosuppressants or immune modulators can be tried with some success, even in children.

Infectious complications

AD of the skin is frequently complicated by bacterial, viral and fungal infections. Immunological aberrations, defective epidermal barrier function and decreased antimicrobial peptides all contribute to an increased susceptibility to infections. Prolonged application of TCS may also play a role.

Clinically, bacterial and viral infections develop rather abruptly during the course of AD and are more common in severe cases. Fungal infections, on the other hand, tend to develop insidiously and are not usually clearly evident at the start.

Bacterial infection

Eczematous lesions of AD are commonly complicated by bacterial infections. The fact that *Staphylococcus aureus* is colonized in over 90% of AD skin lesions explains this phenomenon well, although in practice, the culture rate of *S. aureus* appears to be a little lower than this. In Korean patients, this bacterium has been found in about 63% of AD lesions. Impetigo lesions caused by *Streptococcus* are also common.

Any skin area can be affected, but involvement of the face, especially the perioral area below the nose, is frequently seen. An oozing or yellowish crusted patch develops quite suddenly

over the eczematous skin in this area, and rapidly spreads to the neighbouring skin. A folliculitis pattern is also common in the hair-bearing area. Regional lymphadenopathy, as a secondary infection, is commonly associated and can frequently lead to the aggravation of AD symptoms. After 1–2 weeks of oral and topical antibiotics, together with wet compresses, the lesions usually improve. The first-generation oral cephalosporins are normally effective, but if the lesions are localized, only topical mupirocin ointment can be used.

When AD symptoms flare up suddenly, with the appearance of widespread crusting and oozing patches suggestive of superimposed bacterial infections – sometimes with accompanying fever, patients often respond well to a 1-week-long treatment with systemic antibiotics.

Viral infections

Eczema herpeticum

The most severe infectious complication is eczema herpeticum (EH), which is caused by the herpes simplex virus.^{40–42} Generally, patients with severe eczema will be affected by EH quite suddenly. A few vesicular lesions develop initially but they soon erode and weep, with some pustulation. These lesions spread very rapidly (within 1–2 weeks) to the neighbouring eczematous skin, with extensive areas of grouped vesicular or crusted patches showing over the face and neck, and sometimes the extremities (Fig. 5). The blisters of EH are disseminated and distinctly monomorphic, although later, punched-out erosions become the distinguishing features.

In severe cases, widespread haemorrhagic, eroded or thickly crusted lesions are observed with constitutional symptoms, such as fever and headache. Secondary bacterial infection may also occur and severe and disseminated EH can be complicated by meningitis and encephalitis.

Fortunately, this complication generally responds well to systemic antiviral treatment, although EH recurs several times in some patients. Systemic antiviral therapy should be started as soon as possible to avoid possible dissemination of the herpes virus. Aciclovir, orally or intravenously, is effective and in adult patients with EH, valaciclovir or famciclovir is recommended orally for 7 days.⁴³ Oral antibiotics are usually given together to control bacterial superinfection. If EH occurs around the eyes, ophthalmological consultation is necessary.

Molluscum contagiosum

Skin-coloured, flat-topped or often umbilicated papules commonly develop in children with AD.⁴⁴ They have a predilection for the flexures, but any area can be affected. They can also be spread easily to other parts of the body by scratching (autoinoculation).

The lesions can be removed easily by mechanical expression with tweezers or curettage, although the accompanying pain can make this procedure very difficult in infants and children. Applying a topical anaesthetic cream 30 min to 1 h beforehand can make this procedure easier. For those who cannot bear the pain, topical immunotherapy using

imiquimod cream directly on the lesions can be tried safely with some success.⁴⁵ However, the complete disappearance of the lesions can take time if using immunotherapy.

Superficial fungal infection

When lesions no longer show improvement with routine care and topical treatment with TCS, or else become gradually aggravated and spread peripherally, the possibility of superficial fungal infections must be considered.^{46,47} Tinea pedis is a common complication of prolonged application of TCS, although tinea faciale can sometimes occur as well. Upon close inspection, an active scaly border typical of fungal infections can easily be seen, and a KOH direct smear from the active border can confirm the presence of a fungus. Topical antifungal agents for 2–4 weeks can easily cure the lesions.

Some patients show severe facial lesions that do not respond to TCS, TCIs or even topical antifungal agents. These cases may be due to *Malassezia* infection and patients may show a positive prick test reaction to its extracts.^{48,49} These patients can respond dramatically to 2 weeks of oral itraconazole. There have been controversies about the role of *Malassezia* infection and the use of antifungal therapy against it in head and neck lesions of AD, but clinical improvement by these antifungal agents could support a role of *Malassezia*.⁵⁰

Clinical pearls

- AD skin is frequently complicated by bacterial, viral and fungal infections. Oozing or yellowish crusted patches from bacterial infections develop quite suddenly over eczematous skin. Oral and topical antibiotics for 1–2 weeks can improve symptoms.
- The most severe infectious complication is EH. A few vesicular lesions develop initially, and within 1–2 weeks, spread very rapidly to eczematous skin, which subsequently shows extensive areas of grouped vesicular or crusted patches. This problem generally responds well to systemic antiviral treatment together with oral antibiotics and topical therapies.
- When lesions gradually become aggravated and spread peripherally, despite continuous treatment, the possibility of superficial fungal infections must be considered. *Malassezia* can play a role in severe head and neck dermatitis.

Outlook and future perspectives

AD is quite variable in its clinical manifestations, but has typical clinical features regardless of the ethnicity and age of a patient. Still, we need to develop more specific diagnostic criteria for use in clinical and basic research as the selection of patients based on a phenotypically homogeneous group is very important.

AD is associated with defects both in cellular immunity and epidermal barrier function. This is the reason why AD skin is frequently complicated by infections. Skin affected by eczematous lesions must be actively well maintained with topical treatment. TCS, TCIs and other routine measures should be used properly, not only to mitigate or treat AD symptoms; but also to break the vicious cycle of AD. Infectious complications should be treated as soon

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as possible to prevent further aggravation. Many promising drugs are under investigation,⁵¹ and hopefully more specifically targeted therapy will be available soon.

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Figure legends

Fig 1. The eczematous lesions typically start around the perioral area. Copyright © 2006 Galderma S.A. All rights reserved.

Fig 2. Periauricular eczematization. Acknowledgement: Diepgen TL, Yihune G *et al.* *Dermatology Online Atlas*.

Fig 3. Flexural areas typically affected during atopic dermatitis. Copyright © 2006 Galderma S.A. All rights reserved.

Fig 4. Nipple eczema is quite a specific symptom of atopic dermatitis in females. Acknowledgement: Diepgen TL, Yihune G *et al.* *Dermatology Online Atlas*.

Fig 5. Eczema herpeticum. Acknowledgement: Diepgen TL, Yihune G *et al.* *Dermatology Online Atlas*.





