SEVERE ATOPIC DERMATITIS/ECZEMA — A REVIEW OF THE LITERATURE

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ABSTRACT
Severe atopic dermatitis/eczema (SADE) is an uncommon and potentially debilitating condition with the tendency to follow a persistent course under certain circumstances. Confirmation of the diagnosis and assessment of the extent of impairment in everyday activities and psychosocial functioning is essential. Surveillance is required to ensure early diagnosis and optimal control of comorbid atopic manifestations including food allergies, allergic rhinitis and asthma. Early, aggressive intervention in childhood SADE (e.g. restoration of the skin barrier, reduction of allergen penetration and sensitisation) may prevent progression of the ‘atopic march’ and the consequential development of comorbid disease. Complications of SADE may be severe, such as bacterial and viral superinfection, erythroderma, sight-threatening ophthalmological disease, growth retardation, adrenal insufficiency and substantial psychological distress. A stepwise approach to management is essential to ensure that all avenues are explored prior to initiation of potentially harmful therapeutic regimens. Exacerbating factors should be actively excluded (e.g. non-compliance, use of unproven complementary remedies, secondary infection, hypersensitivity reactions to topical treatments, etc.). Active management (possibly including phototherapy or systemic immunomodulators) may be required to establish control, but may induce substantial side-effects. Patients and their families should be included as well-informed members of the therapeutic alliance, with the aim of accomplishing long-term favourable outcomes in physical as well as psychosocial dimensions.

INTRODUCTION
Severe atopic dermatitis/eczema (SADE) affects a minute proportion of the population, with a profoundly negative impact on their health-related quality of life. Management is challenging and requires an in-depth knowledge of the disease, possible complications, available modes of intervention and empathy for the suffering of the patients and their families.

DIAGNOSIS
Patients with confirmed atopic dermatitis/eczema (ADE) are considered to have SADE if the following features are present:

- 30% of body surface area (BSA) (1% BSA equals surface area of one hand) affected by xerosis, incessant itching, erythema +/- excoriation, extensive lichenification, bleeding, oozing, cracking and alteration of pigmentation
- Everyday activities and psychosocial functioning severely limited, nightly loss of sleep
- Moderate dermatitis with acute changes and significant impact on quality of life.

SADE may present as severe intermittent disease (multiple acute flares/exacerbations) or severe persistent disease (chronic severe disease).

PREVALENCE
SADE accounts for 2% of children and 12-15.7% of adults suffering from ADE in European-based studies.6-8 ISAAC studies indicated a 3.8% prevalence among 6-7-year-old children, 2.1% among 13-14-year-old children in Polokwane and 3.8% among 13-14-year-old ADE patients in Cape Town.9 No data are available on the prevalence of SADE in South African adults.

COURSE AND PROGNOSIS
SADE tends to follow a persistent course, and poorer outcomes are predicted under the following circumstances:

- Early onset, severe, widespread disease
- Comorbid respiratory allergic disease and food-allergies
- Sensitisation to house-dust mite or raised total-IgE levels
- Age-inappropriate patterns of distribution
- Biparental atopy or ADE in other family members
- Patients residing in urban areas

Active management of SADE with topical immunomodulators, phototherapy or systemic immunosuppressants may be the only means of altering the natural history of this condition.2,5,16

Comorbidities
ADE is often the first manifestation of the ‘atopic march’ and patients may present with asthma (30-60%), allergic rhinitis (35-66%) or food allergies (40% of children and 15% of adults with SADE). As patients with SADE have an increased risk of acquiring comorbid disorders, early intervention to restore the skin barrier, reduce allergen penetration and sensitisation, may prevent progression of the ‘atopic march’. Clinicians caring for SADE patients need to ensure that comorbid conditions are diagnosed and adequately controlled.

COMPLICATIONS
Bacterial superinfections (Fig. 1)
Staphylococcus aureus is most frequently implicated as a common trigger of exacerbations.13 This organism not only serves as an infective agent, but is also responsible for direct immunological stimulation via polyclonal T-cell activation due to superantigen production.

Levels of S. aureus colonisation and presence of antistaphylococcal enterotoxin B IgE antibodies correlate significantly with disease severity.19,21 Signs suggestive of superinfection include weeping, crustsing, ADE failing to respond or rapidly worsening on adequate therapy and constitutional symptoms (fever, malaise, lymphadenopathy). The use of diluted bleach baths, followed by rinsing with fresh water, application of emollients and topical

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anti-inflammatories are recommended to reduce heavy colonisation. Intranasal mupirocin or neomycin/chlorhexidine ointment will eradicate nasal carriage. Oral fluclxacinil is considered the antibiotic of choice, and clindamycin, co-trimoxazole or minocycline may be utilised as alternatives. Extensive topical mupirocine or fusidic acid plus diluted corticosteroid led to a significant reduction of skin colonisation and improvement of the skin condition even in clinically uninfected eczema. A steroid-saving effect was postulated as the therapeutic effect was superior when combination antibiotic treatment was applied compared to corticosteroids alone. No significant increase was noted in S. aureus resistance to topical antimicrobials.

Viral infections

Disseminated cutaneous Herpes simplex infection leads to eczema herpeticum (EH) which is associated with fever, malaise, vesicles and widespread punched-out erosions which may develop a haemorrhagic crust. Patients with SADE are at increased risk of developing EH. The mortality rate for untreated EH is reported to be between 6% and 10% and oral or intravenous acyclovir is indicated in severe cases.

Erythroderma

Erythroderma is a widespread, severely erythematous, exfoliative dermatitis involving more than 90% BSA. It may be caused by conditions including drug allergy, seborrhoeic dermatitis, contact dermatitis, lymphoma, leukaemia or psoriasis. The condition may arise in worsening or unstable ADE or be triggered by infection. Erythroderma may be complicated by disturbances in thermoregulation, electrolyte and fluid homeostasis, bacterial superinfection (e.g. Staphylococcal scalded skin syndrome), hypoalbuminaemia, oedema, cardiac failure and death. Hospitalisation is usually required and outcome is improved by early, aggressive therapy.

Ophthalmological complications

Atopic keratoconjunctivitis (AKC)

AKC may be associated with SADE and with sight-threatening corneal scarring. Aggressive intervention includes topical anti-inflammatories or systemic immunosuppressants. Keratoconus and H. simplex keratitis may coexist.

Keratoconus

This rare, progressive, non-inflammatory, degenerative disorder of the cornea leads to gradual corneal thinning, protrusion and progressive irregular myopic astigmatism and significant impairment of sight. It is associated with ADE and considered partly to be the result of chronic rubbing of the eyes.

Atopic cataracts

Rapidly evolving, most frequently bilateral, posterior subcapsular cataracts occur in 10% of patients with long-standing SADE. Use of corticosteroids promotes the development of cataracts.

Spontaneous retinal detachment

This sight-threatening condition is more common in patients with SADE than in the general population and requires vigilance to ensure early diagnosis and successful treatment.

Growth retardation

SADE impairs growth velocity independently of corticosteroid use and is related to eczema severity, chronic stress and sleep disturbance. The corrected height-for-age is below expected values in 10% of these patients. Growth parameters should be carefully monitored and SADE optimally controlled in order to maximise ‘catch-up’ growth.

Adrenal insufficiency (AI)

Silent adrenal suppression or acute adrenal insufficiency (AAI) may be induced by systemic absorption of topical corticosteroids in children (and possibly in adults). Risk is increased by use of high-potency topical corticosteroids, prolonged or frequent application, use of occlusive dressings (especially wet wraps), extensive areas of application (especially in thin-skinned areas) or when the prescribed dosage is exceeded. These effects are amplified in infants and young children, when barrier function is severely impaired and systemic corticosteroids are co-administered (especially with repetitive ‘steroid bursts’ or prolonged courses followed by abrupt discontinuation). The local prevalence of AI is unknown, but a recent Food and Drug Administration (FDA) review regarding adverse drug events following topical corticosteroid administration in children (0-16 years) reported 8 cases.

AAI may be triggered by sepsis, trauma, burn wounds or surgery and the clinical presentation is often non-specific, e.g. lassitude, weakness, dizziness, fatigue, nausea, vomiting, orthostatic hypotension and tachycardia. If the condition is not recognised and appropriate therapy instituted, adrenal crisis may be provoked leading to dehydration, hypothermia, shock, confusion, coma and death.

Integrity of the hypothalamic-pituitary-adrenal (HPA) axis may be evaluated by dynamic function testing.

Psychosocial aspects

The degree of psychosocial impairment of SADE patients probably overshadows most other complications, as it affects all dimensions of psychosocial functioning adversely. Sleep deprivation leads to chronic somnolence, mood changes and irritability which complicate relationships...
with parents, siblings and peers. Children are often embarrassed by their physical appearance. Insensitive comments, teasing and bullying frequently cause social isolation and may lead to depression or school avoidance. Severe limitations of lifestyle are imposed, particularly in respect of clothing, staying with friends, owning pets, swimming or the ability to play or do sports. Restrictive diets related to food allergies and intolerances as well as symptoms suffered due to inadvertent exposure further impair the child’s quality of life. Academic performance is hampered as a result of impaired concentration, use of sedating antihistamines and the frequent coexistence of attention deficit disorder.

Caregivers may experience feelings of hopelessness, guilt, anger and depression as treatment regimens are often complicated, costly, time-consuming and frequent disturbance of sleep leads to exhaustion. The adult SADE patient bears similar burdens and may suffer from shyness and social withdrawal because of their appearance. Occupational functioning is often severely impaired and under extreme conditions occupational changes or application for disability grants may be necessitated.

DIFFERENTIAL DIAGNOSIS

An alternative diagnosis should be considered when ADE is unusually severe or persistent, response to optimal therapy is poor, severe and recurrent infections coexist (especially deep-seated abscesses or pneumonia) or systemic manifestations of disease unrelated to ADE are present. The age of the patient should be kept in mind when a differential diagnosis is considered. Referral is usually indicated under these circumstances. Table I lists considerations for the differential diagnosis.

TRIGGERS AND EXACERBATING FACTORS

Prior to initiation of second-line treatment for SADE, clinicians must ensure that severe, refractory disease is not a result of avoidable or treatable exacerbating factors (e.g. non-compliance, use of unproven complementary remedies, secondary infection, hypersensitivity reactions to topical treatments, exposure to triggers of disease flares, etc.).

TREATMENT MODALITIES

All patients suffering from refractory SADE should be referred to a specialist dermatologist or allergist experienced in the utilisation of phototherapy and other immunomodulatory therapies. Collaboration with a paediatrician, physician or rheumatologist may be helpful in respect of the potential side-effects of second-line therapy. Adherence to a stepwise approach to therapy is essential to ensure that all avenues of therapy are explored prior to initiation of potentially harmful therapeutic regimens. The most frequently utilised therapeutic options are:

Phototherapy

This has been extensively studied and utilised in all age groups. Narrowband UVB (311-313 nm) is the preferred form of phototherapy for refractory, chronic SADE, while the less readily available UVA1 (340-400 nm) may be more effective for the management of acute severe exacerbations. Frequently reported side-effects include erythema, pruritus, acute burns, xerosis and reactivation of *H. simplex*. PUVA (psoralen and UVA-320-400nm) seems to be more efficacious than UVA1 as it decreases disease severity more rapidly, extensively and induces a longer remission period, but the risk of melanoma and squamous cell carcinoma is increased as a result of deeper penetration of UV waves. The strict photoprotection period following administration of the photosensitising agent is an inconvenience to patients.

Systemic immunosuppressants (Table II)

Role of systemic corticosteroids in SADE

A course of 5-10 days of systemic glucocorticoids (e.g. prednisolone 0.5-2 mg/kg in children and 5-60 mg in adults) is often used as ‘rescue/steroid burst therapy’ to abort acute exacerbations. Discontinuation may be followed by rebound flaring and optimisation of topical therapy is essential to prevent this phenomenon. No more than three short courses of steroid therapy per year are recommended as steroid side-effects will ensue.

Corticosteroid treatment continuing for more than 3 months is regarded as long-term therapy and patients receiving ≥5 mg/day in this group require calcium (1 500 mg/day) and vitamin D (800 IU/day) supplementation and a bisphosphonate if osteopenic. Systemic glucocorticoids are not recommended for the long-term management of SADE and strongly discouraged in the paediatric population because of the high risk of significant adverse effects (including HPA-axis suppression, growth suppression, avascular necrosis of the hip, osteoporosis, hyperglycaemia, hypertension, cataracts, lymphopenia, etc.)

Immunotherapy

The administration of subcutaneous (SCIT) or sublingual (SLIT) allergen immunotherapy is controversial in SADE. A combination of cyclosporin and SCIT using house-
Dust mite extract in sensitised SADE patients was administered to 9 patients for a 12-month period. Significant improvement of SCORAD values was noted and cyclosporin therapy could be discontinued in 4 patients within 8 months.

**Biologics and novel therapies**

Omalizumab (anti-IgE), rituximab (anti-CD20), infliximab (anti-tumour necrosis factor [TNF]-alpha antibodies), etanercept (TNF receptor antagonist) and extra corporeal photopheresis (irradiation of mononuclear cells followed by re-infusion) are some of the newer, mostly experimental therapeutic options.

**Nutritional supplementation**

High dose omega-3 (docosahexaenoic acid-5,4 g/day) administration in adult SADE patients led to significant improvement in SCORAD values while...
administration of 1 600 IU cholecalciferol (vitamin D) for a 60-day period showed benefit as well, although risk of hypervitaminosis is substantial and potentially serious.29,42,43 A recent Cochrane review warns that evidence of benefit for nutritional supplementation is limited and discourages recommendations for use.44

CONCLUSION

SADE imposes a heavy burden on patients, their families and health services. Fortunately new avenues of intervention are being actively explored and insight is expanding regarding the impact and management of this debilitating disease. It is crucial that the benefit of these advances be brought to suffering patients at all levels of society.

Declaration of conflict of interest

Attendance at ALLSA 2011 Congress sponsored by Cipla.

REFERENCES

TOPRAZ - a jewel in the control of chronic atopic asthma in adults and children >2 years

Montelukast
Recommended by South African and International Guidelines for the control of persistent asthma in both adults and children > 2 years\textsuperscript{1,2,3}

References:

Reg. Nos. 43/10.2.2/0785; 43/10.2.2/0786; 43/10.2.2/0787. Each tablet contains montelukast sodium equivalent to 4 mg, 5 mg or 10 mg montelukast respectively. Dr. Reddy’s Laboratories (Pty) Ltd. Reg. No. 2000/014145/07. Tel: +27 11 324 2100. www.dreddys.co.za

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