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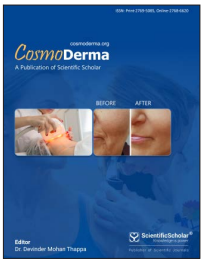

*Review Article*

# Overcoming challenges in management of atopic dermatitis: Role of oxidative stress in the pathogenesis and treatment target of atopic dermatitis (ROAD)

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## ABSTRACT

The Dermatology Advisory Board on Atopic Dermatitis from Asian Medical Expert Academy compiles current evidence–based approach review in managing atopic dermatitis (AD) among Asians. Electronic searches were performed to retrieve relevant published paper, systematic reviews, and guidelines on AD in the period of 2010–2020. A premeeting survey was performed prior to the meeting to gather opinions from experts to identify the individual unmet demands in the current management, and the possible strategies to overcome these issues. Collective opinions are scrutinized during the next step in a meeting, with the establishment of the opinions into an updated consensus in current AD management. Meeting of all committees through webinar platform in 2020 is called in making the current position in the AD management. Current challenges in AD management include steroid phobia, compliance, myths among the community, frequent flares leading to loss of patience, and good rapport. The Expert Panel recommends a stepwise approach to treatment based on disease severity. The use of moisturizers is recommended across all levels of AD severity. Oxidative stress is recognized as an important contributor to AD that can directly damage skin cells and induce an immune response that leads to AD. Prescribed Emollient Device (PED) with antioxidants can help mitigate the effects of oxidative stress in causing AD. Furfuryl palmitate is an antioxidant that has demonstrated efficacy in managing symptoms of AD in adults and children, as well as other inflammatory dermatoses. PEDs can potentially play an important role in the treatment of AD by augmenting "upstream" treatment. This could potentially help reduce the risk of side effects and adverse events in patients undergoing treatment for AD. Furfuryl palmitate is an antioxidant that has demonstrated efficacy in managing symptoms of AD in adults and children.

**Keywords:** Atopic Dermatitis, Prescription emollient devices (PED), Consensus, Oxidative stress

## INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by intense pruritus and eczematous lesions. It commonly associates with other atopic conditions such as rhinoconjunctivitis, asthma and food allergy. It is a common, relapsing chronic inflammatory skin disease commonly occurs in early childhood.[1,2]

The most detrimental clinical symptom is persistent itching, and it leads to further skin damage by physical scratching and thus creates a vicious cycle of "itch-scratch cycle," as more scratching creates more itch. Other symptoms consist of xerosis (dry skin), patchy eczema more commonly seen on flexural surfaces, exudation in superimposed infection, skin thickening in chronic phase of disease and skin discoloration due to pigmentation changes after inflammation.[3,4]

Atopic dermatitis is considered one of the most common chronic conditions.[2,5,6] Up to 20% of children and 8% of adults in most countries live with AD. Since 70s, most industrialized nations have 2–3 folds of increase in AD incidences. In Hong Kong, we share a similar disease burden of overall prevalence of 2–5% population affected by this disease. It is estimated that 30% of Hong Kong children (approximately 160,000 children) have eczema.

It is estimated global prevalence of 230 million and increasing, particularly in many parts of the world like Africa, Asia, Western Europe, and parts of Northern Europe. The disease burden is huge and clinical challenges require multidimensional approaches.

Management of the disease is often complex, it needs (a) Patient/Parent education, (b) Elimination of exacerbation factors, (c) Restoration of skin-barrier function, and (d) At the same time tackling AD associated comorbidities. In children 67–82% have mild AD; 12–26% have moderate AD; only 4–7% have severe AD, severe AD is more frequent in adults.[7,8]

The Dermatology Advisory Board on Atopic Dermatitis from Asian Medical Expert Academy compiles current evidence-based approach review in managing AD among Asians.

## MATERIAL AND METHODS

Electronic searches were performed to retrieve relevant published paper, systematic reviews guidelines on AD in the period of 2010–2020. A premeeting survey was performed prior to the meeting to gather opinions from experts to identify the individual unmet demands in the current management, and the possible strategies to overcome these issues. Collective opinions were scrutinized during the next step in a meeting, with the establishment of the opinions into an updated consensus in current AD management. The meeting recordings were referred to capture all discussion points. These were, thereafter, referenced accordingly with updated scientific material. Meeting of all committees through the webinar platform in 2020 is called in making the current position in the AD management.

## DISCUSSION

### Pathogenesis and impact of AD

Atopic dermatitis pathogenesis is complex and multi-fac torial.[3,9,10] There are some commonly attributed to several factors: skin barrier abnormality, immunological factors. The disease process is further undermined by the persistent disturbance from the ongoing pruritus and the physical damage to alleviate the itch by scratching. The pathological process can be illustrated by the trinity of factors involved in AD pathogenesis.[1]

A recent observation in AD research is that oxidative stress plays a central role in the pathogenesis of this chronic relapsing skin disorder. Events that lead to skin barrier defects have also been correlated with the release of reactive oxygen species (ROS), which directly damage the skin's cellular components, such as the cell membrane, organelles, and even DNA.[11]

The current disease model of AD [Figure 1][3] can perhaps be best exemplified by the trinity of factors involved in AD pathogenesis.[10]

- Extrinsic/allergic AD exhibits high total serum IgE levels and the presence of specific IgE for environmental and food allergens. Barrier disruption promotes production of chemokines which attract Th2 cells*. Intrinsic/non-allergic AD exhibits normal total serum IgE levels and the absence of specific IgE. These abnormal immunological arrays are characterized by lower expression of Th2 cytokines, IL-4, IL-5, and IL-13 with normal serum IgE levels; higher expression of Th1 cytokines, interferon.
- Skin barrier abnormalities can contribute to desiccation and a reduction of protection against foreign insults. Skin dryness can be caused by a decrease in skin ceramides, changes in pH of the outermost layer of skin, overexpression of enzymes

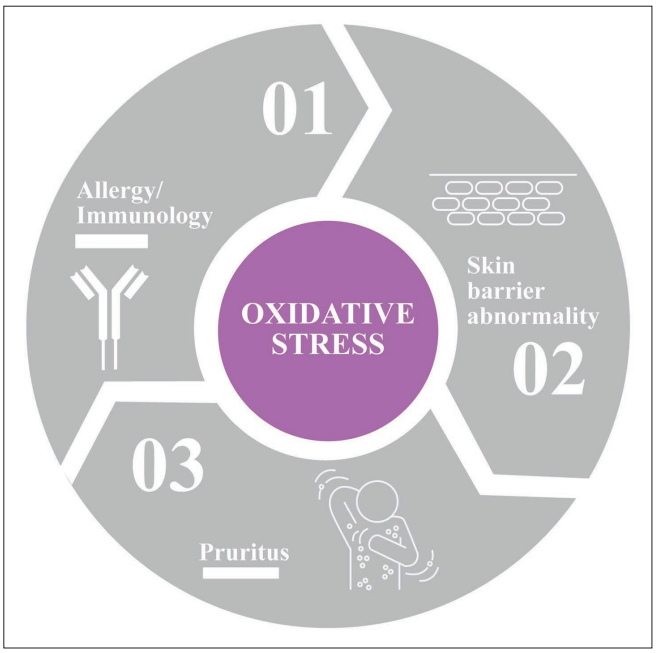


**Figure 1:** Current disease model of AD.

such as kallikreins (KLKs) and chymases, and finally defects in filaggrin.

- A variety of mediators induces pruritus, including histamine. It is correlated with increased plasma concentrations of nerve growth factor. Scratching directly disrupts skin barrier functions. Pruritus itself can lead to Th2 movement into the affected area.

Recently, oxidative stress is also implicated in AD pathogenesis.[3] Oxidative stress occurs when the formation of ROS in a cell exceeds the cell's capacity to remove them. It promotes tissue inflammation through upregulation of genes involved in the production of pro-inflammatory cytokines.

## The impact of AD

Among all the morbidities from AD, the most distressful symptom affected by the disease is pruritus. Nonetheless the disease has a profound impact on the quality of life, this includes sleep disturbance, work and academic performance, even mental health among others. 51.3% of patients with AD has limited their lifestyle, 39% of them tend to avoid social interaction and 43.3% impacted activities.[12–14]

Apart from the physical effects of AD on the patient, the condition also bears profound social and economic costs.

Direct costs of AD[15] medications constitute the majority of direct costs for families of children with AD. AD affects both patients with AD, and society, by increasing taxpayer contributions to disability and healthcare.

Indirect costs of AD are also significant. This is attributed to decreased productivity of the patient and the caregiver[15] such as absenteeism, presenteeism, loss of employment among many other social and psychological burdens.[15]

Embarrassment that may prevent patients from going to work or social gatherings.[15]

In one study ($n$ = 26), more than fifty percent of parents stated that adults and children avoided interacting with children affected by the disease.[16]

About 32% of participants in a study ($n$ = 2002) believed that atopic eczema affected their school or work life.[16]

## Diagnostic criteria for AD

Clinicians in Asia commonly refer to diagnostic criteria published by Hanifin and Rajka.[17] It consists of four major and 23 minor criteria. AD is diagnosed when three major and three minor criteria are met [Table 1].

**Table 1:** Diagnostic criteria for AD

| Major criteria | Minor criteria | Exclusions |
|---|---|---|
| • Pruritus<br>• Dermatitis affecting flexural surfaces in adults and the face and extensors in infants<br>• Chronic or relapsing dermatitis<br>• Personal or family history of cutaneous or respiratory atopy | • Features of the so-called "atopic facies": facial pallor or erythema, hypopigmented patches, infraorbital darkening, infraorbital folds or wrinkles, cheilitis, recurrent conjunctivitis, and anterior neck folds<br>• Triggers of atopic dermatitis: foods, emotional factors, environmental factors, and skin irritants such as wool, solvents, and sweat<br>• Complications of atopic dermatitis: susceptibility to cutaneous viral and bacterial infections, impaired cell-mediated immunity, immediate skin-test reactivity, raised serum IgE, keratoconus, anterior subcapsular cataracts<br>• Others: early age of onset, dry skin, ichthyosis, hyperlinear palms, keratosis pilaris (plugged hair follicles of proximal extremities), hand and foot dermatitis, nipple eczema, white dermatographism, and perifollicular accentuation | • Scabies<br>• Seborrheic dermatitis<br>• Contact dermatitis (irritant or allergic)<br>• Ichthyoses Cutaneous T-cell lymphoma<br>• Psoriasis<br>• Photosensitivity dermatoses<br>• Immune deficiency diseases<br>• Erythroderma of other causes |

## Challenges in AD management

Poor adherence to treatment is the major reason for treatment failure. This is a multifactorial phenomenon that prevails globally and the factors contributing to poor adherence are depicted in Figure 2.[18-21] The Advisory Board committees highlighted the current challenges in their clinical management, in the level of significance, steroid phobia as most significant, followed by compliance issue, patients resort to myths among the community, frequent flares leading to loss of patience, and lastly establishment of good rapport.

In addition to adherence to treatment, factors associated with disease onset and worsening should be taken into account. Exposure to environmental factors including allergens and stimuli in the workplace and daily environment, life-style factors, and temperature, in addition to dysregulation of physiological changes in skin function are associated with maintenance and exacerbation of dermatitis. Warm and hot environment, sweating, wool fibers, psychological stress, food, alcohol drinking, and the common cold are considered to be particularly important as induction and exacerbating factors of itch in AD.

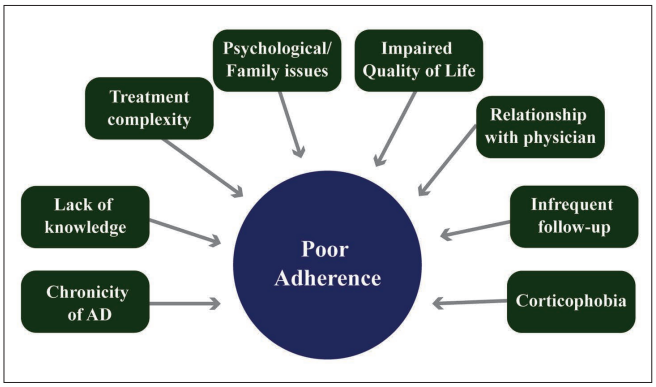


**Figure 2:** Factors contributing to poor adherence.[19,20,21]

### Treatment recommendation for atopic eczema

The goal of treatment is to reach and maintain a state in which symptoms are absent or mild without being disturbed in daily activities by the disease and drug therapy is not required. Even when this level is not reached, the objective is to maintain a state in which symptoms are mild without rapid exacerbations that affect daily activities.

Treatment measures for AD basically consist of drug therapy, skin care for physiological abnormalities in the skin and investigations/elimination of exacerbating factors based on its pathogenesis. These measures are important and are adequately combined for individual patients based on the grade of symptoms and background.

Atopic dermatitis is a multifactorial disease involving genetic predispositions. There is currently no treatment that can completely cure this disease. However, in the lesion site, a further inflammation-related reduction in skin barrier function, enhanced irritability and scratching-related stimuli deteriorate eczema, leading to viscous cycle of inflammation. Therefore, controlling inflammation by drug therapy will also reduce AD-exacerbating factors.

### Topical corticosteroids (TCS)

Currently, topical corticosteroids (TCS) and topical calcineurin inhibitors are used to provide adequate attenuation of inflammation in AD. Their efficacy and safety have been examined in numerous clinical studies.

TCS are often used as a first-line anti-inflammatory topical agent for both children and adults. However, the unregulated and inappropriate use of steroid have led to wide range of side-effects and discourage patients and parents to comply. The phenomenon of steroid phobia as a result, is the biggest hurdle in successful clinical management.[22]

The introduction of calcineurin inhibitors enable clinicians and patients to apply non-steroid topical treatment for mild or limited severity of eczema. But it also bears black box warning for possible safety concern and products are limited to patients aged above two years old.[2,23,24] The new cristoborole topical cream is available in Hong Kong, the clinical benefits are yet to be proven and familiarized by clinicians together with the consideration of cost.

The global consensus guide in appropriate use of different armamentaria would follow the stepwise algorithm. Different global guidelines emphasize that topical treatment should be reinforced for best compliance and, regular use of moisturizers should be emphasized at all stages of diseases.

### Topical moisturizers

The use of moisturizer products plays an important role in all stages of AD. It improves moisture content in the stratum corneum and leads to the prevention of allergen invasion and relapse of dermatitis, as well as suppression of itching by recovering and maintaining skin barrier functions. Moreover, skin care with moisturizers immediately after birth and thereafter, decreases the risk of onset of AD.[25]

It is especially recommended to apply moisturizers immediately after bathing. Topical moisturizers should be applied all over the body including sites that appear to be normal. Continuous use of moisturizer products even after achieving remission of dermatitis with topical anti-inflammatory drugs is also useful to maintain the remission.

Emollients should be used on the whole body both when the atopic eczema is clear and while using all other treatments. With better understanding in the role of good barrier function in the prevention and management of acute stage of AD, the use of emollients has extended to wide variety of unperfumed emollients to use every day for moisturizing, washing, and bathing. Ideally, leave-on emollients should be prescribed in large quantities (250–500 g weekly) and easily available to use at nursery, preschool, or school.[26] With this regard, the use of emollients in most AD populations are grossly under-used.

### The concept of Prescribed Emollient Device (PED)

Why need prescription for non-pharmacological measures? Good examples in modern clinical practice can take references from exercise prescription and dietary advice on prescription.

During the prescription of emollients, physicians can show how to apply emollients, including how to smooth emollients onto the skin rather than rubbing them in. While the application in everyday care is left to the parents and patients, the expert group agree that the clinicians can review repeat prescriptions of individual products and combinations regularly, for example at least once a year to ensure that therapy remains optimal.

Prescribed Emollient Devices are used to prevent transepidermal water loss (TEWL) and to improve skin hydration in patients with AD. PEDs are different from

OTC moisturizers in that they are FDA-approved, devices that provide a structural role in skin barrier function by specifically targeting defects in skin barrier function that are observed in AD; they do not exert their effects by any pharmacological actions like the anti-inflammatory mechanisms in steroids.[27] They are generally applied to the skin 2–3 times daily depending on the specific agent. In this way PEDs can augment "upstream" AD treatment options by acting as an intermediate treatment between emollients and TCS.[27]

### *Commonalities across current consensus and different guidelines for AD*[2,23,24]

The current treatment guidelines and commonalities in practice guidelines are summarized in these two charts [Tables 2a and b]. The advisory board give unanimously highest (100%) consensus on recommending emollients use at all stage of disease (mild to severe), in active flare, remission and in maintenance with inactive disease. With the proven clinical value of this role, clinicians should encourage and supervise patients to achievement a better compliance in moisturizer use [Figure 3 and Table 3]. With the current arena of potent therapeutic modality like immunosuppressants, biologics, and small molecules like Janus kinase (JAK) inhibitors addressing different specific immune abnormalities and effectively controlling clinical symptoms as well achieving better clinical outcomes, moisturizers still play a strong role in up-keeping the barrier integrity and remission maintenance.

### Oxidative stress and AD

The relationship between oxidative stress and cutaneous disorders Skin as the largest organ in our body positioned as a major target of oxidative stress due to ROS generated in keratinocytes in response to environmental and pro-oxidant agents.[3] In normal skin, the epidermis contains higher concentrations of antioxidants than the dermis.[28] Free radicals are generated during normal metabolism are an

**Table 2a:** Treatment approach in children

| Treatment Approach in Children | | | |
|---|---|---|---|
| **Baseline**<br>**Basic therapy** | **Mild**<br>**SCORAD <25 / or transient eczema** | **Moderate SCORAD 25–50 / or recurrent eczema** | **Severe SCORAD >50 / or persistent eczema** |
| Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)<br><br>Emollients used at every stage | Reactive therapy with topical gluco-corticosteroids class II [b] or depending on local cofactors: topical calcineurin inhibitors [b], antiseptics incl silver, silver coated textiles | Proactive therapy with topical tacrolimus [b] or class II or III topical gluco-corticosteroids [c], wet wrap therapy, UV therapy (UVB 311 nm) [a], psychosomatic counselling | Hospitalization, systemic immuno-suppression: cyclosporine A [c], methotrexate [c], azathioprine [c], mycophenolate mofetil [a, c] |

AD: atopic dermatitis, EADV: European Academy of Dermatology and Venereology, SCORAD: scoring of atopic dermatitis, Refer to guideline text for restrictions, especially for treatment marked with [a], Licensed indication are marked with [b], off-label treatment options are marked with [c]

**Table 2b:** Treatment approach in adults

| Treatment approach in adults | | | |
|---|---|---|---|
| **Baseline**<br>**Basic therapy** | **Mild**<br>**SCORAD <25 / or transient eczema** | **Moderate SCORAD 25–50 / or recurrent eczema** | **Severe SCORAD >50 / or persistent eczema** |
| Educational programmes, emollients, bath oils, avoidance of clinically relevant allergens (encasings, if diagnosed by allergy tests)<br><br>Emollients used at every stage | Reactive therapy with topical gluco-corticosteroids class II[b] or depending on local cofactors: topical calcineurin inhibitors[b], antiseptics incl. silver, silver coated textiles[a] | Proactive therapy with topical tacrolimus [b] or class II or III topical gluco-corticosteroids [c], wet wrap therapy, UV therapy (UVB 311 nm) [a], psychosomatic counselling, climate therapy | Hospitalization, systemic immuno-suppression: cyclosporine A [c], short course of oral gluco-corticosteroids [b], dupilumab [a, b], methotrexate [c], azathioprine [c], mycophenolate mofetil [c], PUVA 1; alitretinoin [a, c] |

AD: atopic dermatitis, EADV: European Academy of Dermatology and Venereology, PUVA: psoralen and ultraviolet A, SCORAD: scoring of atopic dermatitis, Refer to guideline text for restrictions, especially for treatment marked with [a], Licensed indication are marked with [b], off-label treatment options are marked with [c]

integral part of normal skin function and do little harm.[3] However, increased or prolonged free radical action can overwhelm antioxidant defense mechanisms and contribute to skin disorders [Figure 4].

Oxidative stress on the skin is known to influence various cutaneous diseases, including atopic dermatitis, contact dermatitis, and psoriasis.[28]

Atopic dermatitis has been associated with increased levels of lipid peroxidation and decreased presence of antioxidants.[29] It was found that children with AD excrete higher levels of oxidative stress markers in their urine, and have significantly less blood antioxidant capacity.[3] Oxidative stress can directly damage skin cells and induce an immune response that leads to AD[3] [Figure 5].

Anti-oxidation is an important concept in targeting the barrier repair among inflammatory dermatoses including AD. Furfuryl palmitate (FP) is a potent antioxidant.[27] FP is an ester obtained when furfuryl alcohol reacts with palmitic acid. It is lipophilic and therefore has high permeability potential through biological membranes. In vitro studies have demonstrated remarkable ROS quenching property.[27] FP is efficacious in treating AD symptoms in children as well as in adults.

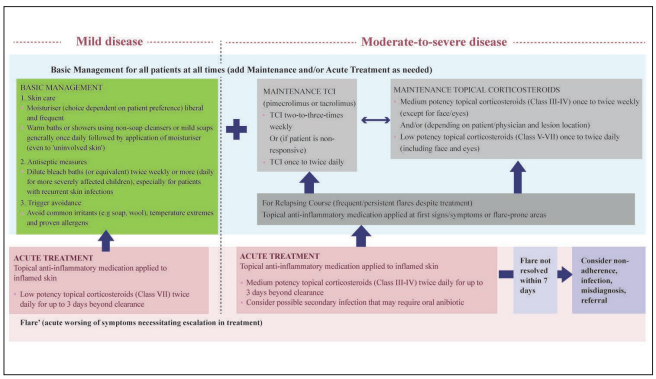


**Figure 3:** Treatment Guidelines for AD.[2,23,24] AD- atopic dermatitis; TCI- topical calcineurin inhibitors.

In children with AD between 3 and 11 years (N = 17),[30] FP use was associated with reduced intensity of blisters, erythema, dryness, desquamation, and itching after 48 hours, 7 and 14 days after initiation of treatment.

In adults with mild to moderate AD[27] more were assessed to have been "cured" or "improved" at day 21 when prescribed FP ($n = 20$) compared with control treatment ($n = 20$, $P = 0.001$).

Furfuryl palmitate is also efficacious in reducing symptoms associated with allergic contact dermatitis.[31] FP use was associated with a mean reduction in symptoms at clinical observations undertaken after 48 hours, 7 days, and 14 days of treatment. About 85% of investigators thought that the efficacy and tolerability of the product were good or excellent.

In patients with AD, FP has efficacy approaching that of corticosteroids. When tested against corticosteroids.[32] Patients with AD on their hands were prescribed either FP-containing cream ($n = 20$) or TCS ($n = 20$). The number of patients who were assessed to have "improved" or been "cured" at the end of the study in both groups was similar.

Professor Pellacani from the Advisory Board shared his experience with using emollient devices enriched with antioxidants, including FP and vitamin E. For example, in an open-label, uncontrolled trial carried out at the Dermatology Department of the University Hospital of Modena, Modena,

**Table 3:** Commonalities across different guidelines for AD[2,23,24]

| Moisturisers and emollients | Topical corticosteroids | Topical calcineurin inhibitors | Antimicrobials | Systemic or phototherapy |
|---|---|---|---|---|
| • Are recommended by guidelines as the mainstay of AD treatment<br>• Improve skin barrier function and hydrate the skin, reducing dryness<br>• Are recommended to be used liberally and frequently for optimal treatment of AD irrespective of severity | • Are considered as first-line anti-inflammatory and immunosuppressant treatment<br>• Are applied on inflamed skin according to needs<br>• Are associated with depression of adrenal function when used in highly potent formulations<br>• Are associated with other adverse effects including secondary infections and skin atrophy | • Are non-steroidal immunomodulatory agents<br>• Come in two forms: tacrolimus ointment and pimecrolimus creams<br>• Are approved for use in patients with moderate to severe AD<br>• Lack epidemiological data to determine if TCIs can cause malignancies (skin cancers and lymphomas) | • Help reduce the density of *S. aureus* colonisation in patients with AD, which is associated with clinical severity<br>• Are not recommended for routine use due to risk of antimicrobial resistance | • Are reserved for patients who have severe AD, do not respond to topical treatments, develop side effects to earlier lines of treatment |

AD: atopic dermatitis, TCI: topical calcineurin inhibitors, TCS: topical corticosteroids

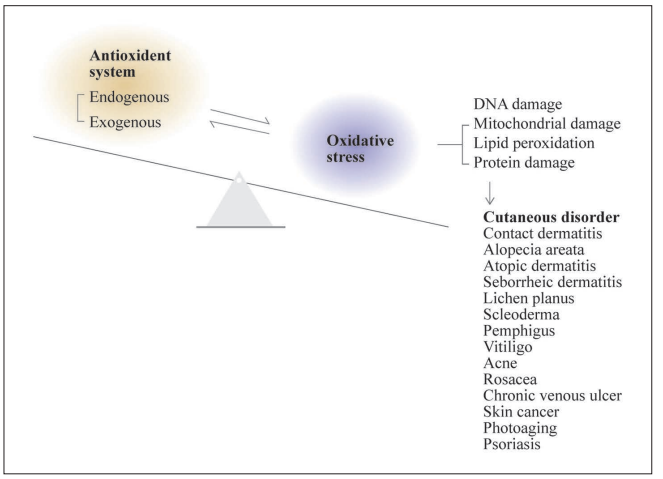


**Figure 4:** Oxidative stress has been defined as a state of imbalance wherein reactive oxygen species overwhelm the capacity of the intrinsic antioxidant systems to inhibit cellular damage due to oxidation.[28]

Italy, he showed clinical results following use of Relizema™ cream. In this study, following 28 days' twice-daily administration, statistically significant reductions were found on the primary endpoint, Investigator Global Assessment scores (rated on a 0–4 scale, where 4 is "severe"), from the baseline mean score reflecting mild-to-moderate disease, to a mean score of "almost-clear-to-mild" at Day 14, and "almost clear" at Day 28. Similar improvements were found at Days 14 and 28 on the secondary endpoints, including eczema severity (as calculated with the Eczema Area and Severity Index) and pruritus intensity (as evaluated with a visual analogical score). Patients also reported a statistically significant improvement in quality of life at the end of the trial (as evaluated with the Dermatology Life Quality Index). Overall, it was found that skin condition improved in over 90% of patients on both investigator-rated and patient-rated assessments. Additionally, no safety issues were identified and most patients reported satisfaction with the product characteristics and ease of use.[33]

Asian guidelines recognize FP as an agent for improving AD symptoms.[17] In the guideline it states that moisturizers with antioxidants, such as vitamins, polyphenols, FP and grape seed oil with antipruritic agents, have been shown to significantly improve AD symptomatically at the same level as TCS. More trials will be available showing its effects on epidermal permeability barrier function in the future.

## CONCLUSION

The advisory board unanimously give highest consensus on recommending emollients use at all stage of disease (mild to severe), in active flare, remission and in maintenance with inactive disease. With the proven clinical value of this role, clinicians should encourage and supervise patients to achievement a better compliance in moisturizer use.

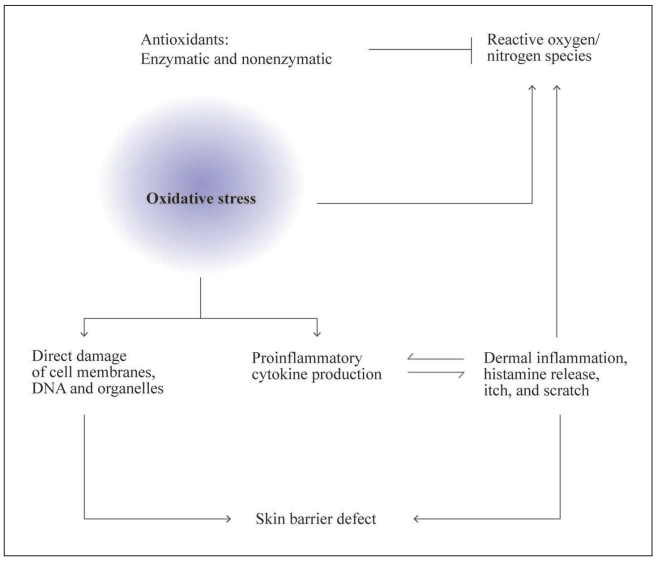


**Figure 5:** Management of oxidative stress.[3]

Amid the ongoing COVID-19 pandemic, the advisory board highlighted that it is prudent to give strong moisturizer advice and emollient prescription, for a better infection control and fight against possible irritant or chemical damages to skin barrier from soap, detergents, and disinfectants.

### Declaration of patient consent

Patient's consent not required as there are no patients in this study.

### Financial support and sponsorship

Nil.

### Conflict of interest

Lisa Braganza, is APAC–Regional Medical Manager In Menarini Asia–Pacific Pte Ltd, Singapore.

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