SPECIAL ARTICLE

Guidelines on Management of Atopic Dermatitis in India: An Evidence-Based Review and an Expert Consensus

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Abstract

Background: Atopic dermatitis (AD) is a common and chronic, pruritic inflammatory skin condition that affects all age groups. There was a dearth of consensus document on AD for Indian practitioners. This article aims to provide an evidence-based consensus statement for the management of AD with a special reference to the Indian context. This guideline includes updated definition, etiological factors, classification, and management of atopic dermatitis.

Methodology: The preparation of guidelines was done in multiple phases. Indian Dermatology Expert Board Members (DEBM), recommended by the Skin Allergy Society of India, prepared 26 evidence-based recommendations for AD. An extensive literature search was done in MEDLINE, Google scholar, Cochrane, and other resources. Articles published in the past 10 years were reviewed and recommendations were graded based on the quality of evidence as per GRADE. After forming the initial structure, DEBM met in Mumbai and gave their decisions on an agree and disagree scale with an Indian perspective. Finally, their suggestions were compiled for preparing the article. After DEBM finalized the draft, a treatment algorithm was formulated for the management of AD. Results: DEBM suggested a working definition for AD. The panel agreed that moisturizers should be used as mainstay of therapy and should be continued in all lines of therapy and in maintenance phase. Topical corticosteroids and topical calcineurin inhibitors should be considered as the first line of treatment. Among systemic therapies, cyclosporin should be considered first line, followed by azathioprine, methotrexate, and mycophenolate mofetil. Phototherapy can be an effective alternative. Empirical food restriction was recommended against.

Conclusion: These guidelines should form a reference for the management of patients with AD in an evidence-based manner.

Key Words: Atopic dermatitis, consensus, expert opinion, guidelines

Introduction

Nomenclature

Indian Dermatology Expert Board Members (DEBM), who formulated the guidelines, agreed to use the term “atopic dermatitis” (AD), which can be used as a synonym for “atopic eczema” or “endogenous eczema.”

Why does India need a guiding tool for AD?

Globally, there are many guidelines established for AD. All guidelines have their own region-specific recommendations based on the ethnic, socioeconomic, resource-based, and demographic characteristics of AD. However, in India there is a paucity of published data about the natural history, etiopathogenesis, epidemiology, clinical patterns, and management of AD. There is yet no guideline on AD from India, published in any indexed journal. This article was developed by the

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Skin Allergy Research Society of India for an updated evidence-based consensus statement for the management of AD, with a special reference to the Indian context.

**Scope of guidelines**

This guideline addresses the management of pediatric and adult AD of all severities. Other forms of dermatitis, such as irritant dermatitis and allergic contact dermatitis, are outside of the purview of this document. The recommendations were prepared to cover an appraisal of all the relevant available literature until May 2018. This guideline is intended for specialists in dermatology, pediatric and adolescent medicine, general medicine, and all groups of physicians whose work includes the treatment of AD in India.

**Methodology**

The preparation of guidelines was projected in multiple phases. An Indian DEBM, recommended by the Skin Allergy Society of India, prepared 26 evidence-based recommendations for AD. An extensive literature search was done in MEDLINE, Google Scholar, Cochrane, and other resources. Articles published in the past 10 years were reviewed and recommendations were graded based on the quality of evidence as per GRADE [Table 1]. After forming the initial discussion proforma, DEBM met in Mumbai. Their discussions were based on literature from clinical research articles and also from their experience and acumen. The members gave their independent views on the preselected recommendations in agree and disagree scale with an Indian perspective [Table 2]. Finally, their suggestions were compiled for preparing the article. After DEBM finalized the draft, a treatment algorithm was formulated for the management of AD.

**Atopic Dermatitis: General Aspects**

**Definition**

AD, also known as atopic eczema, is a chronic, inflammatory, relapsing skin disorder with usually an early age of onset in infancy and early childhood.\(^1\) It follows a relapsing course with repeated exacerbation and remission, which is characterized by dermatitis with itch, and is often associated with elevated serum immunoglobulin (IgE) levels. Natural history of AD often involves typical progression including food allergy, allergic rhinitis (hay fever), and asthma. This sequence of events is referred to as the “atopic march.” It is accompanied in a majority of patients with a personal or family history of “atopic diathesis.”\(^1\)

**Definition of AD:**

**Consensus Statement-I**

Atopic dermatitis is a chronic, recurrent inflammatory skin disease, commonly having a childhood onset and characterized by variably distributed pruritic eczematous lesions with flexural predilection; mostly exhibited by patients with personal or family history of atopic diathesis.

Atopic diathesis: (i) Personal or family history of bronchial asthma, allergic rhinitis and conjunctivitis, and/or atopic dermatitis and/or (ii) predisposition to overproduction of immunoglobulin E (IgE) antibodies.

**Epidemiology**

The cumulative incidence of AD varies between 11% and 21% depending on age and region.\(^2\) In a clinicoepidemiological study in a north Indian pediatric population, the mean age at onset and mean duration of the disease were 4.2 and 3.3 months, respectively, in the “infantile AD” group, and in the “childhood AD” group, the corresponding figures were 4.1 and 1.9 years, respectively. Patients from urban areas significantly outnumbered those from rural background.\(^3\) Another hospital-based north Indian study documented that AD was the most common dermatosis in children registered to a pediatric dermatology clinic with a prevalence of 29.9% of the total patients. The male-to-female ratio was 2.25:1, with a mean onset of 4.5 months. The infants had more of facial involvement and acute eczema, whereas children had nonspecific distribution and chronic eczema, with overall mild to moderate AD being more prevalent. Winter exacerbation was noted in a majority of the population (62%).\(^4\) A lower prevalence 0.42% in the eastern part of the country was reported among dermatology outpatient department attendees.\(^5\)

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**Table 1: Level of evidence and strength of the recommendations**

| Strength of recommendation | Level of evidence                        |
|----------------------------|------------------------------------------|
| A 1 a                      | Systematic review of RCTs, meta-analysis |
| A 1 b                      | Individual RCTs                         |
| B 2 a                      | Systematic review of cohort studies      |
| B 2 b                      | Individual cohort study (including low-quality RCT) |
| C 3 a                      | Systematic review of case-control studies|
| C 3 b                      | Individual case-control study            |
| C 4                        | Case series (and poor-quality cohort and case-control studies) |
| D 5                        | Expert opinion                           |

**Table 2: Recommendation levels**

| Recommendation type | Recommendation strength       |
|---------------------|------------------------------|
| Positive            | Recommended                  |
|                     | Can be recommended           |
|                     | Can be considered            |
| Negative            | Must not be done             |
|                     | Is not recommended           |
Etiology and pathogenesis

Genetic factors

The causes of AD are varied. Both a genetic predisposition and numerous trigger factors play an important role in the first manifestation and in exacerbations of the disease. Major candidate genes reported to date include CTLA4, interleukin (IL)-18, TLR9, CD14, CARD4, PHF11, TLR2, SCCE, MCC, IL-4R, GM-CSF, TIM1, CARD15, GSTT1, SPINK5, eotaxin, TGFβ1, IL-13, RANTES, IL-4, and Fc 3RIb.[6]

Immunological mechanism

In the acute stage, the dominant mechanisms of AD are governed by Th2 cell–related cytokines, such as, IL-4 and IL-13, and chemokines, such as, TARC (thymus and activation-regulated chemokine) and eotaxin.[7] Later, Th1 cells producing interferon (IFN)-γ and IL-12 perform a dominant role in the chronic stage.[8] Langerhans cells and mast cells are also involved in the disease pathogenesis as they express a high-affinity IgE receptor (FcεRI) that causes antigen-presenting cells and mast cells to release histamine, cytokines, and so on. IL-4 and IL-13 stimulate fibroblasts to produce periostin, causing keratinocytes to produce thymic stromal lymphopoietin, which in turn induces TARC/CCL17 production by dendritic cells. In an eczematous lesion of AD, antimicrobial peptides (defensins, cathelicidins, etc.) are inhibited from being expressed by keratinocytes.[9]

Barrier dysfunction

Expression of ceramide and filagrin decreases in skin with AD and is considered as a primary cause of barrier dysfunction. It is also considered as a secondary phenomenon associated with inflammation and as a cause of AD.[6]

Exacerbating factors

Environmental factors responsible for exacerbation of AD vary and include climatic changes, sweating, physical irritation (including scratching), microbes/fungi, contact allergens, stress, and foods.

Atopic dermatitis and vaccinations

It is recommended that children, adolescents, and adults with AD are vaccinated regularly according to the standard national vaccine program recommendation. In an acute exacerbation, postponement of the vaccination until the skin condition has stabilized is recommended.

Course

AD dermatitis has a variable course, and informing patients/parents of the chronic and/or recurrent course is recommended. Spontaneous cure or remission is possible at any time, but about 30% of the children who suffer from the disease may have episodes in adulthood.

Complications

Infections can be frequent complications of AD and include secondary infections with bacteria, virus, and fungi. AD can rarely be complicated with eye diseases (glaucoma, keratoconus, retinal detachment, blindness), alopecia areata, and growth delay. AD can be associated with concomitant ichthyosis vulgaris.

Diagnosis

General aspects

The diagnosis of AD is made clinically and is based on historical features, morphology and distribution of skin lesions, and associated clinical signs. Formal sets of criteria have been developed by various groups to aid in classification.

Diagnostics criteria for atopic dermatitis

Diagnostic criteria proposed by Hanifin and Rajka

One of the earliest and most recognized sets of diagnostic criteria is the 1980 Hanifin and Rajka criteria, which requires 3 of the 4 major criteria and 3 of the 23 minor criteria to be met.[10]

Diagnostic criteria proposed by the United Kingdom Working Party

These consist of one mandatory and five major criteria, it is easy to use and do not require any laboratory testing. The original UK criteria cannot be applied to very young children, but revisions to include infants have since been proposed [Tables 2 and 3]. The Hanifin and Rajka diagnostic criteria were used in 44% of the trials and the UK diagnostic criteria in 12%.[11]

Diagnostic criteria proposed by American Academy of Dermatology

A 2003 consensus conference spearheaded by the American Academy of Dermatology suggested revised

| Table 3: Diagnostic criteria proposed by the United Kingdom Working Party |
|---------------------------------------------------------------|
| **Mandatory criterion (must be positive)**: An itchy skin lesion or parental report of scratching or rubbing of skin |
| **Major criteria (at least three of the five should be positive)** |
| Onset below 2 years of age (not used if the child is less than 4 years of old) |
| History of skin crease involvement (including cheeks in children under 10 years) |
| History of generally dry skin |
| Personal history of other atopic disease (or history of any atopic disease in a first-degree relative of children under 4 years) |
| Visible flexural dermatitis (or dermatitis of cheeks, forehead, or outer limbs in children below 4 years) |
Hanifin and Rajka criteria that are more streamlined and additionally applicable to the full range of ages affected\textsuperscript{[12]} [Tables 3 and 4].

**Disease severity scales for atopic dermatitis**

For the measurement of disease severity, more than 28 different scales were identified, with none of them being the gold standard. The most commonly used severity criteria for AD are the SCORAD index, the Eczema Area and Severity Index (EASI), Patient Oriented Eczema Measure, and the Six Area, Six Sign Atopic Dermatitis severity score.

**SCORAD**

SCORAD is an international severity criterion that has been most popularly adopted in the English written literature at present. SCORAD incorporates both objective physician estimates of extent and severity and subjective patient assessment of itch and sleep loss.\textsuperscript{[13]}

**EASI**

EASI uses only objective physician estimates of disease extent and severity.

**Laboratory investigations for diagnosis**

The diagnosis of AD remains clinical, because there is currently no reliable biomarker available to confirm the diagnosis.

**Serum total IgE level**

A high serum total IgE level is observed in approximately 80% of patients with AD, but is not present in about 20% of the affected individuals. AD was classified into "extrinsic" and "intrinsic" groups based on the presence or absence of IgE elevation; however, this delineation remains controversial. In many, elevation of IgE may be a secondary phenomenon, developed due to epicutaneous sensitization because of impaired skin barrier.

**Allergen-specific IgE levels**

Although patients with AD are known to produce IgE antibodies in response to various allergens such as foods, and pets, these elevations are also nonspecific, because they are found in about 55% of the general population.\textsuperscript{[7]}

**Increases in tissue mast cells and peripheral eosinophil counts**

They have inconsistent association with disease severity.

**Others**

Various studies have shown that serum levels of CD30, macrophage-derived chemoattractant, IL-12, IL-16, IL-18, and IL-31, and TARC may correlate with disease severity scores, but to date none has shown reliable sensitivity or specificity for AD to support general clinical use for diagnosis or monitoring.\textsuperscript{[14]}

**Recommendation for the use of laboratory investigations for diagnosis and assessment of disease severity**

There are no specific biomarkers available for AD that can be recommended for diagnosis and/or assessment of disease severity. Monitoring of IgE levels is not recommended. Routine allergy testing is not recommended as the results show many false positives and less reproducibility. Even with the Phadiatop or the enzyme-linked immunospot (ELISpot) assays, a negative value has a better predictive value rather than a positive value.

**Histopathology**

A skin biopsy taken from a site with acute atopic eczema is characterised by spongiosis, perivascular infiltrates primarily of lymphocytes, and parakeratosis. Chronic eczema is dominated by hyperkeratosis and acanthosis, but sparse lymphocytic infiltrates. Routine skin biopsy is NOT recommended.

**Atopic patch tests**

Skin tests with protein allergens (known as atopy patch test) are not recommended in routine diagnostics.

### Table 4: Diagnostic criteria proposed by the American Academy of Dermatology

| Essential features | Important features | Associated features |
|--------------------|-------------------|--------------------|
| Itch               | Early age of onset| Atypical vascular response (i.e., facial pallor, white dermographism) |
| Eczema with typical morphology and age-specific pattern | Atopy (personal or family history) | Keratosis pilaris, palmar hyperlinearity, ichthyosis |
|                    | Dry skin          | Ocular and periorbital changes |
|                    |                   | Other regional findings (e.g., perioral and periauricular lesions) |
|                    |                   | Perifollicular accentuation, lichenification, and excoriations |

**Controlling Factors Responsible for Exacerbation of AD**

**Food allergens**

There are conflicting evidences available for associations of specific food with AD. Werfel \textit{et al.} concluded a prevalence of food allergy from eight studies proven by double-blind placebo-controlled food challenge studies to be 33%–63%.\textsuperscript{[15]} The common food allergens identified for triggering AD are milk and milk products, peanuts, eggs, soy, wheat, seafood, and shellfish. The DEBM recommended against dietary exclusion for management of AD in patients not having confirmed food allergy (milk or egg). To diagnose a food allergy, clinical symptoms or signs after suspected food allergen intake or exposure must be reproducible, as broad-panel allergy testing unrelated to a clinical
history of a reaction to certain foods should be avoided.

**Recommendation for specific-food-free diet in patients of AD**

- **Level of Evidence (GRADE): 2b**

**Consensus Statement-II**

Food allergens may contribute to eczema. However, empirical food restriction is NOT recommended in patients of atopic dermatitis. The food should be restricted based only on clinical experience and food diagnosis procedures. A specific-food-free diet (especially for infants or toddlers) should only be considered when allergy to the specific food trigger is identified based on proper procedures, including a food diary and allergy test by a specialist.

**Clothing**

Coarse and irritating fabrics causing skin irritation are preferably avoided. Occlusive clothing that can induce heat sensation is not appropriate. Some studies suggest silver-coated textiles can significantly reduce the numbers of *Staphylococcus aureus* and improve the symptoms of AD. Another fabric, derma silk, is also suggested due to its sericin-free composition and nonirritating with antibacterial properties. However, keeping in mind the Indian context, the members suggested use of nonirritant cotton cloths.

**Recommendation for Clothing:**

- **Level of Evidence: 5**

**Consensus Statement-III**

Smooth clothing and avoidance of irritating fabrics and fibers and loose-fitting garments are recommended in patients with AD. Use of woolen, acrylic and nylon fabric should be avoided. Cotton is recommended as best fabric.

**Sweating**

Sweating is an important exacerbating factor for AD, hence washing away sweat by bathing and showering will lead to the improvement of symptoms. Avoiding occupational or recreational exposure to high temperature and humidity can help in controlling exacerbation.

**Environmental factors**

Allergens such as mites, house dust, pollens, and organic solvents such as formaldehyde and toluene can become problematic. Being sensitized to mites in infancy is reportedly a marker for the development of asthma. Periocular pathological changes are often observed during airborne pollen seasons.

**Occupational dermatology aspects**

It is recommended to investigate potential occupational trigger factors of AD in working patients. It is also recommended to reduce potential occupational trigger factors of AD and/or implement skin preventive measures. If hand eczema has already occurred in adolescence in the context of AD, adoption of wet occupations is not recommended.

**Perinatal prevention**

A randomized comparative study revealed that consumption of an elimination diet free of highly sensitized food antigens such as egg and cow milk by pregnant or lactating mothers has NO protective effect on newborns from developing sensitization to food allergens or AD. A meta-analysis provided evidence in support of a moderate role of probiotics in the prevention of AD and IgE-associated AD in infants. The favorable effect was similar regardless of the time of probiotic use (pregnancy or early life) or the subject(s) receiving probiotics (mother, child, or both).

**General Care**

**Bathing**

Bathing and showering are important not only for washing away the components of perspiration but also for washing away allergens, such as, dust and pollens, and microbes on the skin surface. Bathing also allows removal of dirt and debris from the skin and thereby reduces the chance of infection. Swimming should be avoided in acute flares as the amount of free residual chlorine may impact the skin barrier and contribute to AD exacerbation.

**Recommendation for Bathing**

- **Level of Evidence: 3b**

**Consensus Statement-IV**

Once daily bathing with lukewarm water (27 degree Celsius to 30 degree Celsius), which is not too hot and not too cold, for a short period of time (e.g., 5 to 10 min), is recommended preferably during day time.

**Cleansing**

The skin must be cleansed thoroughly, but gently and carefully to get rid of crusts and bacterial contaminants in case of bacterial superinfection. Strong scrubbing or rubbing immediately after bath should be avoided. Skin should be dried using soft towels.
Recommendation for use of Syndet cleansers

- Level of Evidence (GRADE): 4

**Consensus Statement-V**

Use of non-soap cleansers (e.g., Syndet) that are neutral to low pH, hypoallergenic, non-irritant and fragrance free is recommended for AD.

**Avoidance of perfumes, personal hygiene and cosmetic products**

Fragrances, formaldehyde, lanolin, nickel, neomycin, preservatives, such as, parabens, and rubber chemicals are the common contact allergens which should be avoided in products manufactured for use by patients with AD.

Recommendation for avoidance of perfumes and personal hygiene and cosmetic products

- Level of Evidence : 5

**Consensus Statement-VI**

The avoidance of perfumes, personal hygiene and cosmetic products containing solvents such as formaldehyde, and preservatives such as paraben can be recommended particular to the individuals. Perfumed soaps and other toiletries should be avoided.

**Education (patients and parents)**

Patient and parent education is effective in the management of AD and should aim to provide information about the clinical characteristics of AD (etiopathogenesis, clinical manifestations, and disease course in common person language), aggravating and relieving factors, self-management and improving coping skills.

Recommendation for education of the patient or caregiver for better management of AD

- Level of Evidence: 2b

**Consensus Statement-VII**

Education of patient or caregiver is highly recommended at each consultation in the management of AD and should encompass: a. appropriate treatment doses and application frequency; b. how to step up or step down treatment; c. skin care and bathing; d. management of infection. This leads to more effective management of AD and should be reinforced at every consultation.

**Psychological factors and psychosomatic interventions**

Patients with AD often complain aggravation due to stress. Minimizing stress may be helpful in controlling the disease. Psychotherapeutic approaches and behavior therapy can be considered to manage individual emotional factors that trigger AD, such as, vicious itch-scratch cycles, comorbidity with anxiety and depression, and low quality of life (QOL).

Recommendation for recognition of psychological factors and inclusion of psychosomatic interventions in the management of AD

- Level of Evidence: 1a

**Consensus Statement-VIII**

Psychological and psychosomatic interventions are helpful and recommended (if available) for the management of AD.

**Stepladder treatment in atopic dermatitis**

Depending on the severity of the AD, topical treatment methods and/or systemic treatments are recommended. It is recommended to implement stepladder treatment appropriate to the clinical severity. Once remission is achieved, it is advisable to shift to proactive maintenance therapy to reduce the number of subsequent flare ups.

**Oral antihistamines**

Their usefulness is controversial and debated. Published data from randomized controlled trials (RCTs) are available for both sedating and non-sedating antihistamines; the results of these trials generally suggest a limited role for antihistamines in the treatment of AD. Panel members suggested that a subset of patients with AD with allergic rhinitis and bronchial asthma benefit maximum from antihistamines. Sedating antihistamines (cetirizine) may be used short-term, under supervision where itch of eczema causes sleep disturbance especially in children under age of 2 years. Cetirizine also shows steroid-sparing effect. Addressing itch in young atopics is of primary importance. The nocturnal itch that accompanies AD leads to a fall in QOL indices. The active scratching can further disturb the skin barrier function. This will worsen the atopic state. Hydroxyzine and cetirizine will have an ameliorative effect by producing the required sedation and pruritus relief.

Recommendation of use of antihistamines in AD

- Level of Evidence: 1a

**Consensus Statement-IX**

The use of antihistamines is recommended to control pruritus in AD, although their role is limited.

**Use of systemic and topical antibiotic therapy**

In the pathogenesis of AD, there is a significant role of microbial pathogens such as staphylococcus, streptococcus, herpes simplex, molluscum contagiosum, and...
human papillomavirus, and *Malassezia furfur* infection. There is a lack of quality trials to support the use of antimicrobial and antiseptic preparations to treat AD and there were no reports available on the benefit of topical antibiotics/antiseptics, antibacterial soaps, or antibacterial bath additives in clinically uninfected AD.\(^{[26]}\) The DEBM recommends against the indiscriminate use of topical or oral antibiotics and also against the use of combinations of creams of steroids and antibiotics. Secondary infection should be suspected in patients with moderate-to-severe eczema who have weeping dermatitis, folliculitis and overt clinical signs of infection, or who are not responding to first-line topical therapy. Topical antibiotic therapy may be appropriate for localized areas of infection. Systemic antibiotics should be used according to clinical condition.

**Recommendation of use of topical and oral antibiotics in AD**

- **Level of Evidence:** 2b

**Consensus Statement-X**

*Preventive use of topical antibiotic is not recommended. Short courses of topical and systemic antibiotics should be used only with clinical evidence of overt infection. Long-term use of systemic and topical antibiotic therapy should be avoided to reduce the risk of bacterial resistance and sensitization.*

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**Wet wrap therapy**

Wet wrap therapy (WWT) can be helpful to quickly reduce AD severity, and it is often useful for acute flares and/or recalcitrant disease. A recent RCT demonstrated that a 4-week proactive schedule of WWT with diluted topical corticosteroids (TCSs) was superior to WWT with moisturizer in children with severe AD.\(^{[27]}\) The first step of WWT is to apply topical agents to the lesion. Next, the skin is covered with a wet inner layer of tubular bandage followed by a dry outer layer. Gauze or a cotton suit can be used as an alternative. The WWT can be maintained from several hours to a day at a time.

The panel members suggested that its use might not be feasible in every region of India due to varied climatic conditions. However, wherever suitable, it can be used in severe or resistant patients older than 6 months of age, but if used with TCSs it may be associated with the risk of systemic absorption.

**Recommendation of wet wrap therapy in AD**

- **Level of Evidence:** 2b

**Consensus Statement-XI**

*Wet wrap theory with diluted corticosteroids or emollient with moderate to severe AD without risk of infection can be used for the quick reduction of AD severity.*

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**First Line of Therapy**

**Moisturizers/emollients**

Patients with AD suffer from dry skin and defective skin barrier function. Regular use of moisturizer constitutes the core of the management of AD. A moisturizer repairs the skin barrier, maintains skin integrity and appearance, reduces transepidermal water loss, and restores the lipid barrier’s ability to attract, hold, and redistribute water\(^{[28]}\) [Table 5]. Data from RCTs show that moisturizers have a long- and short-term steroid-sparing effect in mild to moderate AD and in preventing AD flares.\(^{[29]}\)

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| Class          | Mechanism of action                                                                 | Mimics natural skin components                          | Examples                          |
|----------------|------------------------------------------------------------------------------------|---------------------------------------------------------|-----------------------------------|
| Occlusive      | Moisturizers influence the skin barrier function of normal skin to reduce TEWL and susceptibility to irritants. | Intercellular lipid bilayers                             | Beewax                           |
|                |                                                                                    | Ceramide                                                | Lanolin                           |
|                |                                                                                    | Cholesterol                                             | Mineral oils                      |
|                |                                                                                    | Free fatty acids                                        | Paraffin                          |
|                |                                                                                    |                                                         | Petrolatum                        |
|                |                                                                                    |                                                         | Propylene glycol                  |
|                |                                                                                    |                                                         | Silicones                         |
|                |                                                                                    |                                                         | Squalene                          |
| Humectants     | Humectants are low-molecular-weight substances with water-attracting properties.  | Natural moisturizing factors in stratum corneum          | Alpha hydroxyl acids              |
|                | They increase water absorption from the deeper epidermis and dermis to the stratum corneum |                                                         | Glycerin                          |
|                |                                                                                    |                                                         | Hyaluronic acid                   |
|                |                                                                                    |                                                         | Propylene glycol                  |
|                |                                                                                    |                                                         | Urea                              |
| Emollients     | They have the ability to instill small droplet of oil into the cracks between desquamating corneocytes in dry skin and consequently to improve the appearance of the skin in terms of softness, flexibility and smoothness. | Natural lipids                                          | Lauric acid                       |
|                |                                                                                    |                                                         | Linoleic acid                     |
|                |                                                                                    |                                                         | Linolenic acid                    |
|                |                                                                                    |                                                         | Oleic acid                        |
|                |                                                                                    |                                                         | Stearic acid                      |

TEWL: Transepidermal water loss
Although no clinical trials have studied the proper amount or frequency of moisturizer use in patients with AD, moisturizer should be used at least twice daily and more frequently during acute flare-ups. Adult patients with AD should use approximately more than 250 g of moisturizer per week.[30] It is recommended to use moisturizer within 3 min after taking a bath while the skin is still moist.

DEBM advised that moisturizers should be used in continuation, even when the AD is clear. It should be part of all treatment phases; mild, moderate, and severe.

Prescription emollient devices (PEDs) are a newer class of topical agents designed to target specific defects in skin barrier function observed in AD. There is limited evidence to suggest that PEDs lessen symptoms and signs of AD, including xerosis and inflammation. The results of few head to head trials of PED versus over-the-counter base moisturizers have shown no statistically significant differences.[31] DEBM discussed the role of PEDs, which are expensive in comparison to moisturizers but can be helpful in selected scenario.

Moisturizers contain ingredients with anti-inflammatory properties that may reduce or substitute the use of TCS, thus minimizing their side effects.[32] An RCT between aloe vera in olive oil cream versus 0.1% betamethasone cream in the treatment of chronic skin lesions following sulfur mustard exposure showed that aloe vera in olive oil cream was at least as effective as betamethasone 0.1% after 6 weeks of applications.[33] In acute inflammatory models, virgin coconut oil showed moderate anti-inflammatory effects on ethyl phenylpropionate-induced ear edema in rats.[34] The main nonglyceride constituents of shea butter have been reported to be triterpene alcohols. With regard to the emollient effect, in vivo and in vitro studies have shown that the biological activities of triterpene acetate and cinnamate esters include anti-inflammatory and anti-tumor properties.[35]

Thus, the most constructive way to spare steroids and avoid steroid-related side effects is through consequent baseline emollient skin care combined with early anti-inflammatory intervention to stabilize the disease and prevent treatment-intensive flares.

Recommendation for use of moisturizer in AD
- Level of Evidence: 1b (steroid sparing action of moisturizer)
- Level of Evidence: 5 (ideal frequency of use of moisturizer)

Consensus Statement-XII

The regular use of moisturizer has short and long term steroid-sparing effects and reduces the frequency of acute episodes.

Moisturizer should be used at least twice a day and should be more frequently used during acute flares.

Topical corticosteroids

Topical corticosteroids (TCSs) are important anti-inflammatory drugs for managing AD, especially during acute stage. TCSs are first-line treatment for patients with AD who have failed good skin care, including moisturizer use.

Efficacy: RCTs have demonstrated safety and continued efficacy of repeated courses of low- to mid-potency TCS on active AD skin until clearance for up to 5 years in children and up to 1 year in adults.[36]

Long-term proactive TCS: The proactive approach of applying low–mid potency TCS twice weekly for the prevention of flares in stabilized AD has been shown to be effective in both adults and children.[37] Proactive treatment (along with reactive) was found to be superior to reactive only management in a year-long RCT in pediatric patients.[38]

Classification: As per British National Formulary Classification, TCSs are classified as very potent, potent, moderate, and mild [Table 6].[39] A variety of factors should be considered when choosing a particular TCS for the treatment of AD, including patient age, areas of the body to which the medication will be applied, and other patient factors such as degree of xerosis, patient preference, and cost of medication.

Long-term TCS adverse effects: When used cautiously, long-term use of low to mid potency TCS is reasonably safe. However, the long term use of TCS, especially if high potency, may cause local side effects, such as, striae rubrae, skin atrophy, telangiectasia, skin burning, erythema and acneiform eruptions. In rare cases, systemic effects may occur including hypothalamic–pituitary–adrenal axis suppression, more frequently in children due to the high ratio of total body surface area to body mass, which is about 2.5 to 3 times higher than for adults.[40] The use of twice-weekly proactive treatment has not been shown to cause skin atrophy.[41]

Dosage: No universal standard exists for quantity of application, although suggested methods include
use of the adult fingertip unit (the amount from the distal interphalangeal joint to the fingertip, or approximately 0.5 g, being applied over an area equal to two adult palms), following the rule of 9’s that measures the percent of affected area and use of charts that propose amounts based on patient age and body site.

**Frequency of application**: Twice daily application of TCSs is generally recommended for the treatment of AD; however, evidence suggests that once-daily application of some TCSs may be sufficient. Proactive, intermittent use of TCSs as maintenance therapy (one to two times per week) on areas that commonly flare is recommended to help prevent relapses and is more effective than use of emollients alone.

### Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCIs) (pimecrolimus and tacrolimus) have been approved since 2002 for anti-inflammatory therapy in AD.

**Efficacy**: RCTs have demonstrated that TCIs are safe and effective when used twice daily for the intermittent treatment of AD flares in children and infants (3 months) for up to 5 years and in adults for up to 1 year.[41] A meta-analysis of 25 RCTs found tacrolimus 0.1% to be as effective as the mid-potency TCS hydrocortisone butyrate 0.1%, whereas tacrolimus 0.03% is less effective than hydrocortisone butyrate 0.1% but more effective than the low-potency TCS hydrocortisone acetate 1%.[42]

**Strength**: There are two available TCIs, tacrolimus ointment and pimecrolimus cream. Both agents have been shown to be more effective than vehicle in short-term (3–12 weeks) and long-term (up to 12 months) studies in adults and children with active disease.

### Table 6: BNF classification of topical corticosteroids

| Class    | Potency | Generic name and strength |
|----------|---------|----------------------------|
| Class I  | Very potent | Clobetasol propionate 0.05% |
| Class II | Potent   | Betametasone dipropionate 0.025% |
|          |          | Betamethasone valerate 0.1% |
|          |          | Diflucortolone valerate 0.1% |
|          |          | Fluocinolone acetonide 0.025% |
|          |          | Prednisolone 0.025% |
|          |          | Hydrocortisone butyrate 0.1% |
|          |          | Mometasone furoate 0.1% |
|          |          | Triamcinolone acetonide 0.1% |
| Class III| Moderate | Alclometasone dipropionate 0.05% |
|          |          | Betamethasone valerate 0.025% |
|          |          | Clobetasone butyrate 0.05% |
|          |          | Fluocinolone acetonide 0.00625% |
|          |          | Fluocortolone 0.25% |
| Class IV | Mild     | Hydrocortisone 0.1%-2.5% |
|          |          | Fluocinolone acetonide 0.0025% |

BNF: British National Formulary

Recommendation for use of TCS in AD

- **Level of Evidence**: 1a

**Consensus Statement-XIII**

- TCSs can effectively relieve AD pruritus
- TCSs have a significant effect in the short term and long term treatment of AD
- TCSs are used as first-line therapy along with appropriate use of moisturizing agents
- During maintenance treatment, TCSs can be applied weekly twice (weekend therapy) to “hotspots” as a proactive management during maintenance
- Adequate and suitable quantities of TCS to be used, should be discussed with the patient attendant/care giver. They should be counseled regarding finger-tip unit.
Systemic corticosteroids

Although systemic corticosteroids (CSs) improve the clinical symptoms of AD, their administration should generally be avoided because of adverse effects and the rebound phenomenon. Their use should be limited to short courses as a transition to a more sustainable treatment. There are no long-term RCTs evaluating efficacy and safety of systemic corticosteroids in AD.

There are two RCTs which studied the efficacy of systemic CS in children. Both the trials were of low quality and none of them studied methylprednisolone, which is the most widely prescribed CS in clinical practice. The Practical Allergy (PRACTALL) Consensus Group guidelines published in 2006 suggested that patients with acute flares may benefit from a short course of systemic CSs, but their long-term use, especially in children, should be avoided. A slow taper is advisable to decrease the risk of rebound. There is no consensus on the duration of the taper, but it should overlap with a steroid-sparing agent. Special consideration should be made with pediatric patients because of concerns with delayed or reduced bone growth.

Second Line of Therapy

Cyclosporine

Cyclosporine (CsA) is an oral calcineurin inhibitor that suppresses the activation of the T-cell transcription factor, nuclear factor of activated T cells, inhibiting the transcription of a number of cytokines, including IL-2. It is approved for the treatment of adults with AD in European countries, Australia and Japan.

Efficacy: Studies in both adults and children have confirmed that cyclosporin is effective in the short-term management of severe AD, at doses of 3–5 mg/kg/day. RCT with 64 proven patients who received CsA had a decrease both in the surface area of involvement and in the degree of inflammation of the remaining dermatitis at the 6 week time mark. Based on seven long-term RCTs, CsA can be recommended as an effective second-line agent for AD for up to 1–2 years in both adults and children 2 years and older.

Dosage and scheduling: CsA is applicable to patients 16 years of age or older with failure/resistance to first-line therapies. The drug should be administered twice a day at a daily dose of 3–5 mg/kg/day. CsA has been shown to be effective and relatively safe in four long-term RCTs in adults who received up to 1 year of continuous treatment. Low starting doses (3 mg/kg/day) and high starting doses (5 mg/kg/day) were found to be equally effective (EASI/body surface area improvement) after 2 weeks.

Adverse effects and monitoring: Irreversible nephrotoxicity, infection, hypertension, electrolyte disturbances, dyslipidemia, tremor, hypertrichosis, headache, gingival hyperplasia, and nonmelanoma skin cancer are the major serious side effects of CsA. Two or more months with serum creatinine more than 30% above baseline may predict irreversible nephrotoxicity.

These adverse effects may occur regardless of daily dosage used, but high dose and low dose groups have only been compared and measured over short periods of time (up to 12 weeks).

Pediatric considerations: CsA is an effective treatment for AD in the pediatric population, similar to adults. Both continuous long-term (up to 1 year) and intermittent short-term dosing schedules (3- to 6-month courses) are efficacious. CsA can be used in children older than 2 years of age. Long-term safety in children has not yet been established and caution should be exercised.
steroids. Few clinical studies suggest that UV-B and UV-A1 are efficacious in the management of AD.\textsuperscript{[53,54]} The use of light therapy may decrease the need for topical steroid and topical immunomodulator use. The common adverse effects include actinic damage, local erythema and tenderness, pruritus, burning, and stinging. Rarer side effects include nonmelanoma skin cancer, melanoma (mostly with PUVA), lentigines, photosensitive eruptions, folliculitis, photo-onycholysis, HSV reactivation, and facial hypertrichosis.\textsuperscript{[52-54]}

There is still no standard protocol for the optimal dose, duration, and frequency of narrowband (NB)-UVB treatment [Table 7]. The optimal treatment dose of UVA1 has not been determined yet. Considering the low accessibility of UVA1 devices compared with other modalities of phototherapy, NB-UVB offers the most efficacious and cost-effective evidence based treatment for patients with chronic AD.

Studies document the safe and effective use of both UVA and UVB phototherapy in children and adolescents.\textsuperscript{[55]} However, there is an increased risk of nonmelanoma skin cancer in children receiving PUVA treatment.\textsuperscript{[56]}

Recommendation for use of Phototherapy in AD

- Level of Evidence : 2a

Consensus Statement-XVII

- UV therapy can be one of useful treatment modalities for moderate to severe AD.
- UVA1 (acute phase) and NB-UVB (chronic phase) are the most suitable phototherapy modalities for AD treatment.
- NB-UVB is the most preferred phototherapy option because of better availability

Azathioprine

Off-label use of azathioprine (AZA) can be considered in adult patients unresponsive to, contraindicated to, or experiencing adverse effect with CsA. Double-blind placebo-controlled studies demonstrate that AZA improves both QOL and signs and symptoms of the disease when used in patients with AD as monotherapy.\textsuperscript{[57,58]}

Measurement of the enzyme thiopurine methyltransferase (TPMT) is recommended before the initiation of treatment. A dose of 1–3 mg/kg/day is recommended depending on TPMT activity.

Nausea, vomiting and other gastrointestinal (GI) symptoms are common while on AZA. The other side effects include headache, hypersensitivity reactions, elevated liver enzymes and leukopenia. There is literature to support the use of AZA to treat AD in the pediatric population, but the dosage and optimal duration of therapy still needs to be defined.\textsuperscript{[59,60]}

Recommendation for use of Azathioprine in AD

- Level of Evidence : 1a

Consensus Statement-XVIII

- Azathioprine should be considered as a second-line choice among systemic immunomodulators in adult patients unresponsive to or experiencing side effects with cyclosporine.

Mycophenolate mofetil

A long-term RCT investigating mycophenolic acid showed similar efficacy to CsA (3 mg/kg/day) in adults after the 10\textsuperscript{th} week of therapy, but a delayed onset of action in the mycophenolic acid group.\textsuperscript{[61]} Insufficient data exist to make recommendations regarding the optimal mycophenolate mofetil (MMF) dosing or duration of therapy for patients with AD.

Recommendation for use of Mycophenolate mofetil in AD

- Level of Evidence : 1b

Consensus Statement-XIX

- Mycophenolate mofetil, administered at a dose of 1.5 g/day or less, has long term safety and can be considered as an alternative immunomodulator in adult patients unresponsive to or experiencing side effects with cyclosporine.

Dosing ranges from 0.5 to 3 g/day. MMF is generally well tolerated, with GI symptoms being the most commonly encountered. Hematologic (anemia, leukopenia, thrombocytopenia) and genitourinary (urgency, frequency, dysuria) symptoms were rarely reported.

Methotrexate

The true efficacy of methotrexate (MTX) in the treatment of refractory AD is unknown, because of inadequate data. In an RCT comparing MTX (10–22 mg/week) with AZA (1.5–2.5 mg/kg/day) in adults with severe AD, both treatments were found to have similar effects on disease severity.\textsuperscript{[62]} Based on only two small long-term RCTs, MTX seems to be a well-tolerated and effective third-line

### Table 7: Guidelines for narrowband UVB according to skin type

| Skin type | Initial UVB dose | Dose increment after each treatment | Maximum dose |
|-----------|------------------|------------------------------------|--------------|
| I         | 130 mJ/cm\textsuperscript{2} | 15 mJ/cm\textsuperscript{2} | 2000 mJ/cm\textsuperscript{2} |
| II        | 220 mJ/cm\textsuperscript{2} | 25 mJ/cm\textsuperscript{2} | 2000 mJ/cm\textsuperscript{2} |
| III       | 260 mJ/cm\textsuperscript{2} | 40 mJ/cm\textsuperscript{2} | 3000 mJ/cm\textsuperscript{2} |
| IV        | 330 mJ/cm\textsuperscript{2} | 45 mJ/cm\textsuperscript{2} | 3000 mJ/cm\textsuperscript{2} |
| V         | 350 mJ/cm\textsuperscript{2} | 60 mJ/cm\textsuperscript{2} | 5000 mJ/cm\textsuperscript{2} |
| VI        | 400 mJ/cm\textsuperscript{2} | 65 mJ/cm\textsuperscript{2} | 5000 mJ/cm\textsuperscript{2} |
| UV: Ultraviolet | | | |

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option for the long-term treatment of moderate-to-severe AD in both children (above 8 years) and adults.

Recommendation for use of Methotrexate in AD
- Level of Evidence: 2b

Consensus Statement-XX
- Methotrexate can be considered as a second-line choice among systemic immunomodulators after cyclosporine.

Fourth Line of Therapy: Biologics and Emerging Therapies

Crisaborole
Crisaborole is a topical phosphodiesterase-4 inhibitor that reduces the production of proinflammatory cytokines. In two short-term (28 days), identically designed, multicenter, phase III studies in this patient population, topical therapy with crisaborole ointment 2% reduced disease severity and pruritus severity compared with vehicle, with the effect established early and sustained over the course of treatment.\(^{[63]}\)

Dupilumab
Dupilumab is a fully human monoclonal antibody directed against the IL-4a receptor a-subunit, which blocks the signaling of both IL-4 and IL-13, the two key drivers of type 2 immune response.\(^{[64]}\) In 2017, dupilumab was approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe AD in patients 18 years of age and older. A systematic review and meta-analysis of efficacy and safety of dupilumab treatment in moderate to severe AD provided evidence that dupilumab had an acceptable safety profile and resulted in clinically relevant improvements in signs and symptoms of AD.\(^{[65]}\)

Omalizumab
Limited data exist to determine the efficacy of omalizumab in the treatment of AD. One double-blind, placebo-controlled study did not show clinical improvement in AD with its use despite reducing free serum IgE levels.\(^{[66]}\) In general, treatment of AD with omalizumab is not recommended.

Other biologicals
On the basis of positive case reports, there is limited experience for the use of ustekinumab, rituximab, tocilizumab, and alefacept in AD. Current evidence does not allow use of these biologicals in AD, except for some exceptional situation.

Apremilast
Apremilast, an oral phosphodiesterase-4 inhibitor, was FDA-approved in September 2014 for the treatment of moderate-to-severe plaque psoriasis. However, its upstream anti-inflammatory effects, ease of use as an oral agent, and mild side effect profile make it an interesting treatment option for AD as well. Multiple open-labeled trials of apremilast in moderate-to-severe AD produce conflicting reports on efficacy, some showing fair and other showing limited efficacy.\(^{[67,68]}\)

Interferon gamma
There are a few studies on IFN-γ that demonstrate its efficacy in the treatment of AD.

High-dose intravenous immunoglobulin
A review of literature showed improvement was observed in 61% of patients with AD treated with high-dose intravenous immunoglobulin (hdIVIg). Adults appeared less likely to respond (48%) than children (90%), and the duration of response was also more prolonged in children. Adjunctive therapy in adults was more effective than monotherapy (59% vs. 0%), whereas monotherapy was effective in 90% of children. HdIVIg may offer a safe potential therapeutic avenue for resistant cases of AD, particularly in children, but should be further assessed using double-blind placebo-controlled trials.\(^{[69]}\)

Recommendation for use of Biologics and Apremilast in AD
- Level of Evidence: 5

Consensus Statement-XXI
- In patients with recalcitrant atopic dermatitis, biologics especially dupilumab or phosphodiesterase-4 inhibitor like apremilast can be used as off-label therapy. However, the costeffectiveness should be seriously considered.

Maintenance Therapy
The proactive use of topical anti-inflammatory therapy to address subclinical inflammation is an effective, contemporary clinical strategy for the management of AD. Systematic review of RCTs reporting efficacy of TCSs and/or TCIs for flare prevention in AD reveals efficacy of proactive treatment with TCS and TCI to prevent AD flares. The trials, however, do not allow firm conclusions about long-term safety beyond 1 year.\(^{[69]}\) Indirect evidence from vehicle-controlled trials suggests that twice-weekly application of the potent TCS may be more efficacious to prevent AD flares than tacrolimus ointment.

Recommendation for proactive treatment with intermittent TCS or TCI in AD
- Level of Evidence: 1a (TCS)
- Level of Evidence: 1b (TCI)

Consensus Statement-XXII
- Proactive treatment with intermittent TCS therapy during long-term follow-up is helpful to reduce acute flares.
- Proactive therapy with tacrolimus ointment is effective to reduce the occurrence of flares.
Adjuvative Treatment

Alitretinoin
Alitretinoin, also known as 9-cis-retinoic acid, is a recently developed retinoid derivative. Alitretinoin is useful for the treatment of chronic hyperkeratotic atopic hand eczema.

Probiotics/prebiotics
Probiotics (Lactobacillus alone or Lactobacillus with Bifidobacterium) appeared to play a protective role in AD prevention upon administration in the pre- and postnatal periods. However, there is no evidence to support the benefit of probiotics in infants.[70]

Essential fatty acids
Diet supplementation with evening primrose oil or an omega-3 fatty acid (docosahexaenoic acid) is safe and may be helpful in AD, but there are still insufficient RCT data assessing clinical efficacy for this method to be recommended.

Vitamin D
RCTs have reported contradictory results for the therapeutic value of vitamin D supplementation in AD. One meta-analysis showed that serum vitamin D level was lower in the patients with AD, and vitamin D supplementation could be a new therapeutic option for AD. Vitamin D has a potentially significant role for improving the symptoms of AD. The results from this study suggest that vitamin D supplementation may help ameliorate the severity of AD and can be considered as a safe and tolerable therapy.[71]

Conclusion
AD has a profound impact on the physical, mental, and social well-being of the patients and the parents. These guidelines suggest a treatment algorithm for patients with AD. However, to achieve high treatment efficacy, compliance, and patient satisfaction, treatment decisions should be made jointly by the treating physician and the patient or parents. It is of paramount importance to consider disease severity, socioeconomic factors, psychological status, and the patient’s desire for treatment, before choosing an appropriate treatment for individual patient with AD.

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**Treatment Algorithm for Atopic Dermatitis**

| Initial assessment of disease history, extent, severity and activity | (Includes family history, background and associated condition like asthma or allergic rhinitis) |
| --- | --- |
| Disease at presentation | Explanation of the disease, patient or parental counseling, behavioral modifications and setting goal of therapy |

**Mild or moderate AD**
- **Moisturizers & Emollients**
- TCS
  - Potent TCS to be avoided in face, flexures & genitalia and beyond 3 weeks
- TCI
  - Pimecrolimus preferred in less than 2 years age and in face, flexures and genitalia

**Severe AD**
- **Moisturizers & Emollients**
- TCS & TCI
  - PLUS
  - Short course (2 weeks and taper) of oral steroid

**Adjuvant Therapy**
- Identification and Avoidance of triggers
- Moisturizers
- Syndet Cleansers
- Oral antihistamines
- Control of Infection: Short course of topical or systemic antibiotics, Antiviral
- Psychosomatic approach

**First Line**
- Cyclosporine
- Azathioprine
- Phototherapy
- MMF,MTX
- Biologics and Apremilast
- Week End TCS (2 days/week), TCI
- Maintenance Phototherapy

**Second Line**

**Third Line**

**Fourth Line**

**Maintenance Therapy**
scientific and financial support for the conduct of expert group meetings.

**Disclaimer**

This guideline reflects the best available evidence at the time of preparation. Adherence to these guidelines may not ensure successful treatment in every situation. The treating physician must make the ultimate judgment regarding the choice of any specific therapy in the context of circumstances for individual case scenarios.

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