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NEW FDA APPROVED DRUGS FOR THE TREATMENT FOR ATOPIC DERMATITIS

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ABSTRACT

Atopic Dermatitis (AD) is a highly pruritic chronic inflammatory skin disease that commonly presents during early childhood. It is a special form of eczematous dermatitis with wide range of severity. Several studies indicate that the disease is very common in western world with lifetime prevalence in children of 10% to 20%. In most patients it occurs before 5 yrs and typically clears by adolescence. AD has an immunologic basis. Both innate and adaptive immune responses are impaired in AD patients. Intense pruritis is a hallmark of the disease which leads to extensive scratching and further breakdown of the skin barrier. Treatment of atopic eczema should be based on a "stepped-care plan" where treatments are stepped up or down depending on the assessment of the state of the child's skin by the physician. Both topical and systemic treatments are given for eczema. Topical corticosteroids and calcineurin inhibitors are used as topical anti-inflammatory agents. Patients should be carefully instructed about the use of topical glucocorticoids to avoid side effects. Newer drugs used in treatment of AD are Crisaborole ointment and Dupilumab injection. FDA approved these drugs on 14th December 2016 and 28th March 2017 respectively.

KEYWORDS: Atopic Dermatitis (AD), Pruritis, Eczema, Dupilumab, Crisaborole.

INTRODUCTION

Atopic Dermatitis (AD) that commonly presents during early childhood is a highly pruritic chronic inflammatory skin disease. It is said to be as synonymous with eczema. Atopic dermatitis is the first manifestation of atopy in several cases. It is associated with personal and family history of respiratory allergy and is shown to have profound effects on patient's lives, career, choices and social interactions.[1,2]

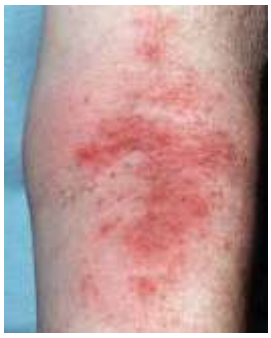


Fig 1: Atopic Dermatitis.

Epidemiology

The disease is very common in Western world .In children it have a lifetime prevalence of 10% to 20%.[3,4]

Etiology

- Allergens, such as dust mites, pollen, molds, or animal dander.
- Harsh soaps or detergents, rubbing the skin, and wearing wool.
- Workplace irritants, such as fumes and chemicals.
- Weather changes, especially dry and cold.
- Temperature changes, such as a suddenly higher temperature. This may bring on sweating, which can cause itching. Lying under blankets, entering a warm room, or going from a warm shower into colder air can all cause itching.
- Stress. Emotions such as frustration or embarrassment may lead to more itching and scratching.
- Certain foods, such as eggs, peanuts, milk, soy, or wheat products, if you are allergic to them. Up to 40% of children with moderate to severe atopic dermatitis also have some type of food allergy. But experts don't agree on whether foods can cause atopic dermatitis.
- Excessive washing. Repeated washing dries out the top layer of skin. This can lead to drier skin and more itching, especially in the winter months when humidity is low.

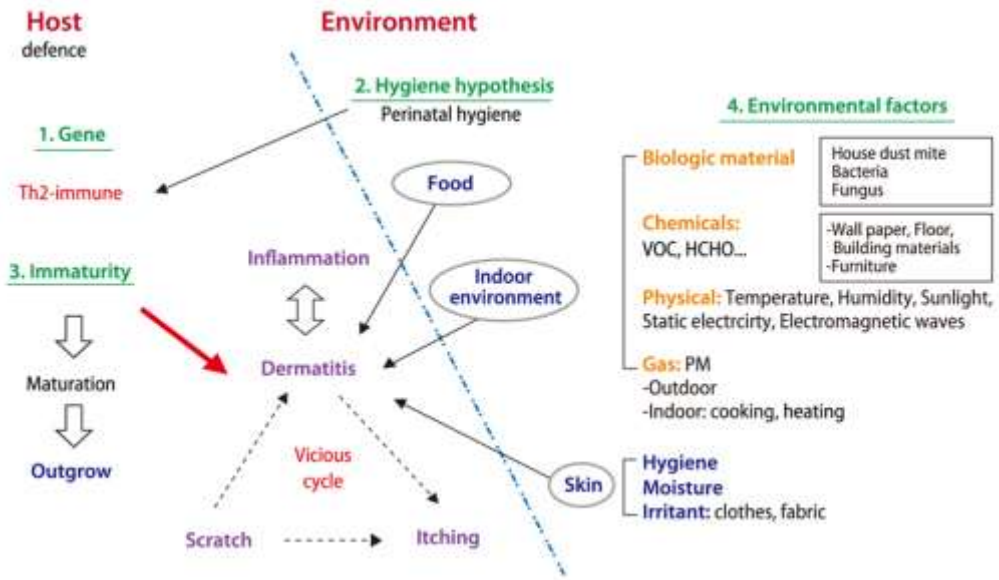


Fig 2: Etiology of AD.

Pathophysiology

AD is multifactorial in origin. In the pathogenesis of AD it was seen that there occurs interactions between susceptibility genes, the host's environment and immunologic factors. It has been observed that primary T cell immunodeficiency disorders are frequently associated with elevated serum IgE levels and eczematoid lesions. Also in AD a primary epithelial barrier defect is observed. The terminal differentiation of the epidermis and formation of the skin barrier is facilitated by a key protein named as Filaggrin. It is the main source of several major components of natural moisturizing factor of the stratum corneum including pyrrolidone carboxylic acid and urocanic acid. The loss of functional gene which encodes for filaggrin is found to be very strong predisposing factors for atopic dermatitis. The patients with fillagrin deficiency experience a reduced level of pyrrolidone carboxylic acid and urocanic acid.[5,6]

Systemic Immune Response

Both innate and adaptive immune responses are impaired in patients with AD. An intact and functional skin barrier is required for an effective cutaneous innate immune response. In AD intense pruritus is a hallmark which inevitably leads to extensive scratching and ultimately leading to breakdown of the skin barrier. When various organisms attack the damaged skin barrier, pattern-recognition receptors- composed of mannan-binding lectins and surfactant proteins recognize unique sugars present on both gram-positive and gram-negative bacteria, fungi, and viruses. They directly activate the complement pathway or act as opsonins by coating the pathogen and make them accessible for phagocytosis. Mannan-binding lectin deficiency predisposes individuals to bacterial and viral infections, including HSV and *S. aureus*. Also a mutation in the Toll-Like Receptor 2 gene R753Q was found in patients with AD which leads to more severe phenotype, higher serum total IgE levels, and greater susceptibility to *S. Aureus* colonization.[7]

Due to impaired neutrophil chemotaxis in response to *S. aureus* the IL-1 receptor pathway has been implicated for defective host immune response to them. Stress-induced release of corticotrophin-releasing hormone and the ensuing reduction of IL-18 and IL-1β levels might also play a role in the susceptibility to cutaneous infections in patients with AD since stress exacerbates inflammatory skin diseases. The level of soluble CD14 was found to be reduced in children with AD when compared with non-atopic children. This results in a reduced capacity to respond to microbial signal. It was studied that various poly-morphonuclear defects occurs in subjects with AD such as impaired phagocytic function and a reduced capacity to produce reactive oxygen species. Also the patients have defective poly-morphonuclear chemotactic activity which makes the disease severe and appearance of cutaneous lesions.[8-10]

Increased homing T cells was found in the peripheral blood of patients with AD which produce interleukin (IL)-4, IL-5, and IL-13 but little interferon (INF)-γ.

- IL-4 and IL-13 induce the expression of vascular adhesion molecule-1 involved in eosinophill infiltration, down-regulate Th1-type cytokine activity and promote the isotype switching to IgE.
- IL-5 plays a key role in the development, activation, and cell survival of eosinophils.[11]
  Increased cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE) enzyme activity is seen in mononuclear cells from patients with AD. This contributes to the increased IgEsynthesis by B cells and the IL-4 production by T cells in AD since production of IgE and IL-4 is decreased in vitro by PDE inhibitors. The expression of the co-stimulatory molecule, CD86, on B cells of AD patients is significantly higher than in normal patients. Anti-

human CD86 significantly decrease the production of IgE by peripheral blood mononuclear cells which is stimulated by IL-4 and anti-CD40mAb.[12-14]

Skin Immunopathology

Cytokine expression

Acute lesions consists predominantly of activated memory T cells and have significantly greater number of cells producing IL-4, IL-5 and IL-13 and are characterized by lymphocytic infiltrate .In chronic AD skin lesions, greater numbers of IL-5, Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) IL-12 and INF-γ mRNA expressing cells are found than in acute AD. These contribute to the increased numbers of eosinophils and macrophages. The increased expression of IL-12 in chronic AD skin lesions is of interest in that cytokine plays key role in IFN-γ production. Its expression in eosinophils and/or macrophages initiates the Th1 or Th0 cell development in chronic AD. Activated T cells infiltrating the skin of AD patients induce keratinocyte apoptosis which causes spongiotic process found in AD lesions.[15,16]

Antigen-presentingcells: Increased number of IgE-bearing LCs found in AD skin appears to play an important role in cutaneous allergen presentation to Th2 cells. IgE-bearing LCs that has captured allergen activates memory Th2 cells in atopic skin. They may also migrate to the lymph nodes to stimulate T cell expansion into the pool of systemic Th2 cells. Normal individuals are highly expressed in the inflammatory environment of AD. This enhances binding and uptake of allergens and activation of LCs upon receptor ligation.[17-19]

Inflammatory cell infiltration

A chemoattractant for CD4+ T cells, is increased in acute AD skin lesions IL-16.Increased levels of C-C chemokines, RANTES(regulated on activation, normal T cell expressed and secreted), monocyte chemotactic protein-4, and eotaxin are found in AD skin lesions and likely contribute to the chemotaxis of eosinophils and Th2 lymphocytes into the skin.[20-25]

Signs and Symptoms

- Pruritis.
- Dry scaly skin.
- Crusted rashes on face, scalp, hands, arms feet or legs.
- Small bumps that open and weep when scratched.
- Redness and swelling of skin.
- Thickening of the skin.[26]

Diagnosis

The American Academy of Dermatology has suggested the following universal diagnostic criteria for atopic dermatitis.

A. Essential features

1. Pruritus.
2. Eczematus changes those are acute, sub-acute, or chronic:

a. Typical and age-specific patterns:

i. Facial, neck, and extensor involvement in infants and children.

ii. Current or prior flexural lesions in adults/any age.

iii. Sparing of groin and axillary regions.

b. Chronic or relapsing course.

B. Important features

1. Early age at onset.
2. Atopy (IgE reactivity).
3. Xerosis.

C. Associated features

1. Keratosis pilaris/Ichthyosis/Palmar hyperlinearity.
2. Atypical vascular responses.
3. Perifollicular accentuation/Lichenification/Prurigo.
4. Ocular/Periorbital changes.
5. Perioral/periauricular lesions.[26]

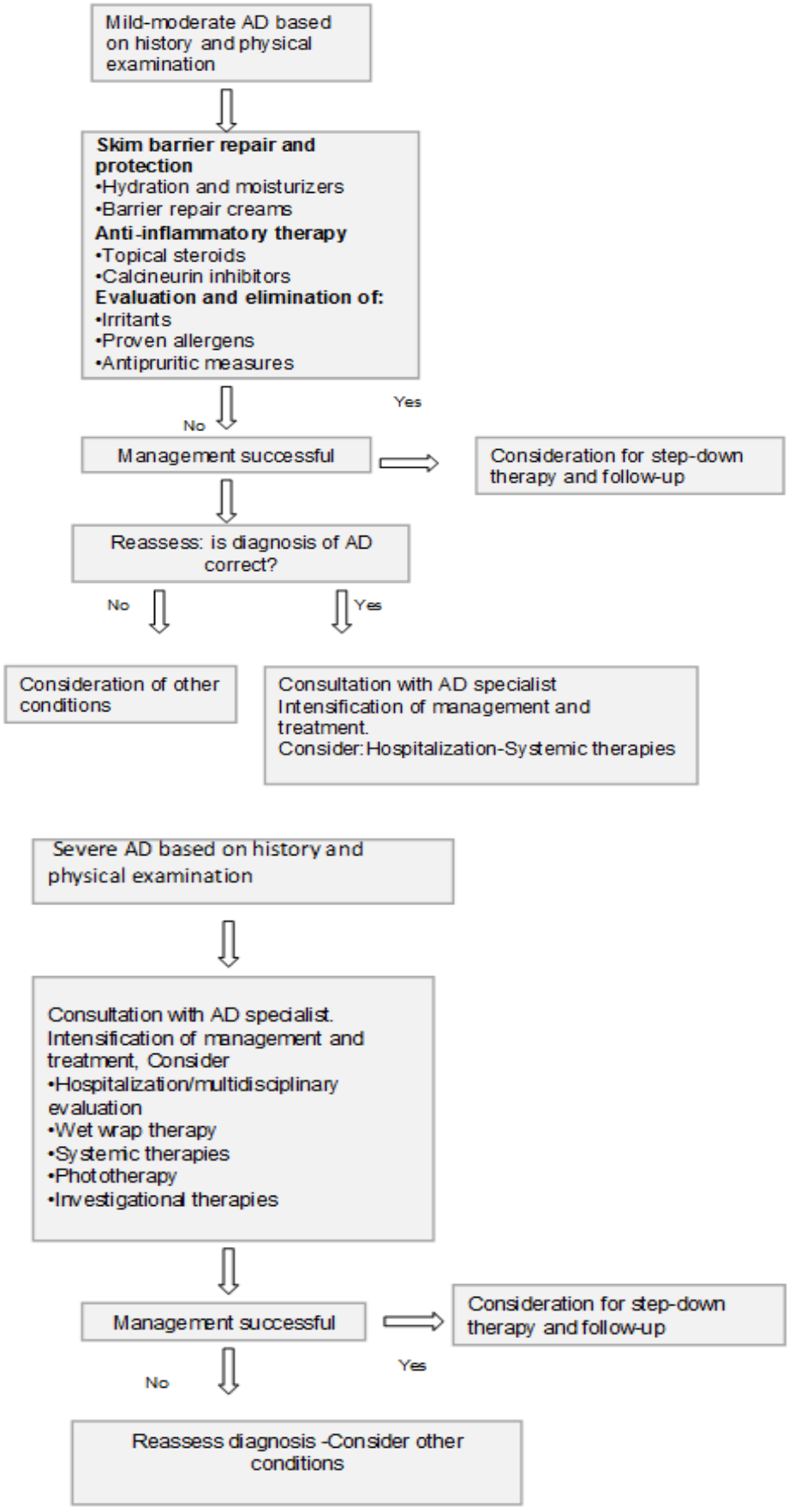
Management

Stepped care plan for eczema is as follows:

Table-1.[27]

STEP 1: Clear skin. Use emolients only.
STEP 2: mild-areas of dry skin, and infrequent itching. Use emollients alone or combined with a topical steroid of mild potency.
STEP 3: moderate- areas of dry skin, frequent itching and redness. Use emollients with a topical steroid of moderate potency (7-14 days, face 3-5 days use), bandages, (then a topical calcineurin inhibitor such as tacrolimus-but only initiated under specialist dermatological supervision).
STEP 4: severe- widespread areas of dry skin, incessant itching, and redness. Use emollients, potent topical steroids (moderate potency on the face or neck),bandages, (then tacrolimus, phototherapy or systemic treatment-but only initiated under specialist dermatological supervision).

The algorithm for treatment of AD is as follows



Topical Treatment

Cutaneous hydration

Due to the reduced ceramide levels and enhanced transepidermal water loss in patients with AD have marked decrease in skin barrier function. This causes dry skin (xerosis) contributing to disease morbidity by the development of microfissures and cracks, which serve as portals of entry for skin pathogens, irritants, and allergens.

Lukewarm soaking baths for at least 20 minutes, followed by the application of an occlusive emollient can give patients excellent symptomatic relief.

Use of an effective emollient combined with hydration therapy will help to restore and preserve the stratum corneum barrier.[28,29]

Topical steroids

The goal is to use emollients to enhance skin hydration and lower-potency glucocorticoids for maintenance therapy.

Topical corticosteroids and calcineurin inhibitors act as topical anti-inflammatory agents. A given concentration of a topical steroid is more potent in an ointment than in a cream. The classification of topical corticosteroids based on potency (according to the active ingredient of the drug and the vehicle) is shown in Table 2.[30,31]

Class I–mild
Hydrocortisone 0.5-1.0% hydrocortisone acetate 0.5-1.0%
Class II–moderate
aclomethasonedipropionate 0.05% betamethasone valerate 0.02% betamethasone valerate 0.05% triamcinolone acetonide 0.02% triamcinolone acetonide 0.05%
Class III–potent
betamethasone dipropionate 0.05% betamethasone valerate 0.1% methylprednisolone aceponate 0.1% mometasonefuroate 0.1%

- Topical glucocorticoids should be applied to the skin lesions and emollients should be used over uninvolved skin.
- A patient should be advised to use mild potency steroids for the face and the neck exception can be made for severe flares which may benefit from short term (3-5 days) use of moderate potency steroids.
- Steroids of moderate potency or potent corticosteroids are indicated for short periods only (7-14 days) for flares in vulnerable sites such as axillae and groin.
- If a mild or moderate topical steroid has not controlled the eczema within 7-14 days, the presence of a secondary bacterial or viral infection should be considered.
- Ultrahigh potency glucocorticoids should be used only for very short periods of time and in areas that are lichenified, but not on the face or intertriginous areas because of their potential side effects.[27]

Topical calcineurin inhibitors

Calcineurin inhibitors (tacrolimus and pimecrolimus) have been successfully used in the treatment of AD.

Pimecrolimus works by inhibiting Th1 and Th2 cytokine production, reducing antigen-presenting capacity of DCs, mast cells and basophils.[32]

Tacrolimus acts by binding to FK binding protein thereby inhibiting the activation of T cells, LCs, mast cells, and keratinocytes.

Unlike topical corticosteroids, tacrolimus ointment does not cause cutaneous atrophy and has been used safely for facial and eyelid eczema. Local burning sensation has been the only common adverse event.[33]

Systemic Therapy

Systemic glucocorticoids

The use of systemic glucocorticoids, such as oral prednisone, is rarely indicated in the treatment of chronic AD. Short courses of oral glucocorticoids may be appropriate for an acute exacerbation of AD.[34]

Intravenous immunoglobulin

Intravenous Immunoglobulin reduces skin inflammation in patients with refractory AD. Since benefits of intravenous immunoglobulin therapy in AD, is of short duration it is essential to intensify local skin care in combination with alternative therapies.[35]

Interferon-γ

Interferon-γ is known to suppress IgE responses and down-regulateTh2 cell proliferation and function. It decrease total circulating eosinophil counts and thus reduce the clinical severity of AD.

Cyclosporine

Cyclosporine is a potent immunosuppressive drug. It acts primarily on T cells by suppressing cytokine transcription. Discontinuation of treatment generally results in rapid relapse of skin disease. Elevated serum creatinine or more significant renal impairment and hypertension are specific side effects that are of concern when cyclosporine is used.[36]

Antihistamines

Non-sedating antihistamines can be used for a month in children with severe eczema or in children with mild/moderate eczema who suffer from severe itching or urticaria. If the outcome is successful it should be continued.[37]

Alternative Therapies

Phototherapy

Phototherapy should be considered when other therapeutic interventions have failed or considered inappropriate or if the patient's quality of life is significantly impaired Broad-band ultraviolet B, broad-band ultraviolet A, narrow-band ultraviolet B (311 nm), UVA-1 (340-400 nm), and combined UV_{AB} phototherapy can be useful adjuncts in the treatment of AD. Through phototherapy IgE-binding epidermal cells, such as mastocytes, dentritic cells and Langerhan's cells have been significantly reduced. Short-term adverse effects with phototherapy may include erythema, skin pain, pruritus, and pigmentation. Long-term adverse effects include premature skin aging and cutaneous malignancies.[34]

Following treatment methods are under research:

- Probiotic bacteria and prebiotic fibers
- Omalizumab immunotherapy
- Allergen specific immunotherapy for AD (only treatment directed in IgE-mediated diseases.)

Newer Drug Therapy

1. The US Food and Drug Administration have approved **Dupixent (dupilumab)** injection for the treatment of adults with moderate to severe atopic dermatitis which is not controlled by topical therapies. It can be used with or without topical corticosteroids. It is usually administered as an injection under the skin.

- **Mechanism:** Dupixent consist of dupilumab a monoclonal antibody as the active ingredient that binds to a protein Interleukin-4 receptor alpha subunit that causes inflammation thereby inhibits inflammatory response which develops Atopic dermatitis.
- **Pharmacokinetics**
  Absorption – Bioavailability: 64%
  Peak plasma concentration: 70.1mcg/ml
  Peak plasma time: ~1 week
  Distribution – Vd: 4.8 L
  Metabolism – Metabolic pathways not established.
- **Safety and efficacy**: Participants who received Dupixent achieved greater response such as clear or almost clear skin and reduction in itch after 16 weeks of treatment.
- **Dosage forms and strength**
  300 mg/2 ml single dose prefilled syringe.
  600 mg (ie, two 300 mg injections) sc once and then 300 mg SC every other week.
- **Side effects**
  Allergic reactions.
  Eye problems - Conjuctivitis, keratitis, redness, itching, eye and eyelid inflammation.
  Injection site reactions.
  Cold sores in mouth or on lips.
- **Contraindications**
  The safety of Dupixent in the treatment of asthma is not established.
  It should not be used in known hypersensitivity to dupilumab or its excipients.
- **Cautions**
  Hypersensitivity reactions including generalized urticarial and serum sickness.
  Conjuctivitis and keratitis
  Asthma
- **Drug interactions**
  Avoid co administration with live vaccines
  Dupilumab modulate serum levels of some cytokines which alters the formation of CYP450 enzymes. Thus monitor for ay side effects when taken with CYP450 substrates.
- **Storage**
  Refrigerate at 36-46 °F.
  Do not freeze, expose to light or shake.
- **Brand name**: Dupixent.[39]

2. The FDA recently approved a novel drug **Crisaborole (Eucrisa)** for the treatment of mild to moderate AD in adults and children greater than age of two.

- **Mechanism:** It is a topical ointment which acts by inhibiting Phosphodiesterase 4 enzyme inhibitor that helps to reduce symptoms of itchiness and inflammation caused by Atopic dermatitis.
- **Dosage and strength :** 2% topical ointment
- **Pharmacokinetics**
  Absorption: Steady state achieved on day 8, peak plasma concentration 127mg/ml.
  Distribution: 97% protein bind.
  Metabolism: Major metabolites 5 -4(cyanophenoxy) 2 hydroxyl benzyl alcohol is formed via hydrolysis and is further metabolised in to down stream metabolite with 5 -4(cyanophenoxy) 2 hydroxyl benzoic acid as the metabolite.
  Elimination: Excreted via urine.
- **Side effects:** Application site pain, burning, stinging, contact urticarial.
- **Contraindication:** In patients who have experienced hypersensitivity to crisaborole.
- **Cautions:** Urticaria, pruritis, sweling, erythema
- **Storage:** At controlled room temp 20-25 ºC.[40]

Non Pharmacological Treatment

- **Topical moisturizers** are used to combat xerosis and transepidermal water loss, with traditional agents containing varying amounts of emollient, occlusive, and/or humectant ingredients. Although they often include water as well, this only delivers a transient effect, whereas the other components provide the main benefits.
- **Emollients** (eg, glycol and glyceryl stearate, soy sterols) lubricate and soften the skin.
- **Occlusive agents** (eg, petrolatum, dimethicone, mineral oil) form a layer to retard evaporation of water, whereas humectants (eg, glycerol, lactic acid, urea) attract and hold water.[36,37]

Recommendations for non-pharmacologic interventions for the treatment of atopic dermatitis

- The application of moisturizers should be an integral part of the treatment of patients with AD as there is strong evidence that their use can reduce disease severity and the need for pharmacologic intervention.
- Bathing is suggested for patients with AD as part of treatment and maintenance; however, there is no standard for the frequency or duration of bathing appropriate for those with AD.
- Moisturizers should be applied soon after bathing to improve skin hydration in patients with AD.
- Limited use of non soap cleansers (that are neutral to low pH, hypoallergenic, and fragrance free) is recommended.
- For the treatment of patients with AD, the addition of oils, emollients, and most other additives to bath water and the use of acidic spring water cannot be recommended at this time, because of insufficient evidence.
- Use of wet-wrap therapy with or without a topical corticosteroid can be recommended for patients with moderate to severe AD to decrease disease severity and water loss during flares.[14]

CONCLUSION

Atopic dermatitis is a severe form of eczema. It is treated by stepping the treatment up or down depending on the assessment of severity of dermatitis by the physician. Physicians should inform the patients with mild to moderate dermatitis that AD is a lifelong illness. Both topical and systemic therapies are given for AD. The new drugs approved by FDA for the treatment of AD are Dupilumab injection and Crisaborole topical ointment. These drugs reduce itchiness and inflammation caused by AD. Treatment using Crisaborole have improved the patient condition than other topically applied drugs. Dupilumab is the first targeted biological therapy approved for the treatment of AD in patients who are inadequately controlled with topical medication. Patients have shown good response towards these drugs in the treatment of AD.

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