Eczema: A Comprehensive view on Treatment Modalities

Shelote C.*, Kubde C., Awandekar N., Umekar M.
Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Dist. Nagpur, Pin 441002

***Abstract*— Eczema is a chronic inflammatory skin condition that has become almost epidemic among children. The therapeutic approach for Atopic Dermatitis (AD) demands for a protracted course of therapy. By introducing the first biologic medication, treatment options for AD recently underwent a radical transformation. Basic, Topical and systemic therapy for AD patients, including children and adults, are the main topics of the modified guidelines that are described here. If conservative measures are unsuccessful in providing enough symptom relief, standard medical care including a pharmaceutical strategy may be required. Recently, proactive treatment methods that include intermittent, daily applications of topical calcineurin inhibitors or low-potency steroids to avoid future flares have received increased attention. Basic therapy concentrates on moisturising topical treatment and avoiding both particular and general provocation factors. Topical glucocorticoids and topical calcineurin inhibitors (TCI)-based anti-inflammatory therapy is utilised for exacerbation management and, more recently, for proactive therapy in some situations. Although tacrolimus and pimecrolimus from the TCI are favoured in some areas, topical corticosteroids remain the cornerstone of therapy. For extreme refractory instances, systemic immune-suppressive therapy is an option. Superinfection and microbial colonisation may exacerbate disease and warrant further antimicrobial therapy. Adjuvant therapy includes exposure to UV light, preferably at UVA1 or UVB 311 nm. Various targeted biologics are also being introduced for AE management and are being touted as effective treatments. This article offers a treatment recommendation and a description of recent research on the management of AD.**

Keywords:- Atopic Dermatitis, Glucocorticoids, Tacrolimus, Pimecrolimus.

I. INTRODUCTION

Eczema is a persistent skin ailment that causes inflammation and reaches practically epidemic proportions. It is typically the initial symptom of atopy and a difficult condition to treat because to its early onset in childhood. Dryness, lichenification, and itchy, red skin are all clinical indicators of eczema (1). In the most recent classification of allergic diseases, which is described in this example of allergy, the term "constitutional dermatitis" is used for atopic dermatitis. There will still be use of the conventional acronym "AD." The name "atopic dermatitis" was first proposed in the 1930s by Wise & Sulzberger.(2)

Different forms of eczema:

There is some evidence that eczema can exist in more than one form, which includes atopic and nonatopic variants, despite the fact that the clinical characteristics of the condition are often consistent. The nonatopic form is not IgE mediated, whereas the atopic form is IgE mediated. Eosinophilia may manifest in either both of the form of eczema. Nummular eczema, seborrheic dermatitis, hand eczema, dyshidrotic eczema, neurodermatitis, contact dermatitis, and status dermatitis are other eczema subtypes.(1)

Pathophysiology

Two theories can be used to explain the inflammatory lesions in atopic dermatitis. The first hypothesis postulates an unbalanced adaptive immune system, and the second hypothesis contends that the skin barrier is compromised. These two hypotheses might not be incompatible with one another and might even complement one another. (3)

1. Immunological Hypothesis: The immunological imbalance theory states that an imbalance of T cells, specifically T helper cell types 1, 2, 17, and 22, as well as regulatory T cells, is what causes atopic dermatitis. In the allergic (atopic dermatitis) condition, the Th2 differentiation of naive CD4+ T cells is predominate, particularly in situations of acute eczema. Interleukin production rises as a result, with the main ones being IL4, IL5, and IL-13, which raise IgE levels and prevent Th1 differentiation.

2. The skin barrier hypothesis: According to the Skin Barrier Hypothesis, those with filaggrin gene mutations are more prone to get atopic dermatitis. The

discovery that individuals with filaggrin gene mutations are at increased risk for developing the illness serves as the basis for this notion. The filaggrin gene encodes structural proteins that help the stratum corneum and stratum granulosum's keratinocytes adhere to one another. As a result, the skin barrier and stratum corneum remain hydrated. Reduced filaggrin production brought on by gene anomalies results in trans epidermal water loss and skin barrier breakdown, which lead to eczema. There is proof to back up the idea that dry skin brought on by a compromised skin barrier makes it easier for allergens to enter the body, leading to allergy sensitization, asthma, and hay fever. Application of emollients may be a key goal of preventing the progression of eczema into allergic airways disease. Early infancy prevention is key for dry skin and active eczema.

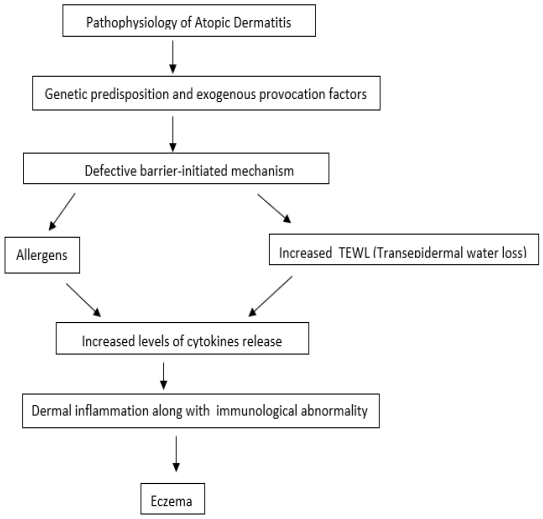


Fig 1. Pathophysiology of the Eczema

II. TREATMENT MODALITIES

The AD management is stratified in three main steps: basic therapy , topical therapy, and systemic therapy. Examples of Basic ,Topical and Systemic treatment modalities for Eczema are depicted in following tables-

Table I- Examples of Basic Therapies

Sr. No.	BASIC THERAPIES
I	Handwashing
II	Salt Baths
III	Coal Tar
IV	UV-Phototherapy
V	Moisturizers

Table II- Examples of Topical Therapies

Sr. No.	TOPICAL THERAPIES
I	Topical Glucocorticoids: Hydrocortisone, Beclomethasone, Fluticasone propionate, Mometasonfuroate
II	Topical Calcineurin inhibitors: Tacrolimus and pimecrolimus
III	Topical antiseptics and antipruritics: Diphenhydramine, Doxepine, 1% pramoxine hydrochloride.
IV	Topical antibiotic : Fusidic acid
V	Topical antiseptics: Triclosan, Povidone Iodine, Octenidin, Sodium Hypochloride.

Table III- Examples of Systemic Therapies

Sr. No.	SYSTEMIC THERAPIES
I	Oral Glucocorticoids: Prednisone, Prednisolone, Dexamethasone
II	Oral antibiotics: Erythromycim, Macrolide Antibiotics, Cephalosporins
III	Oral immunesuppresants: Cyclosporin-a, Methotrexate, Azathioprine, Mecophenolate mofetil.
IV	Biologics therapies: Dupilumab, Nemolizumab, Rituximab.

I. Basic therapy for a disturbed skin barrier function:

a) Handwashing

The majority of medical professionals advise against allowing youngsters with atopic dermatitis to take frequent baths. A natural barrier against is disrupted by frequent washing, especially in hot water, which tends to vanish protective oils from the skin's surface. However, maintaining excellent cleanliness is important since infection can exacerbate atopic dermatitis. Atopic dermatitis is characterised by dry skin, that results into increased transepidermal water loss and decreased water-binding capacity. The skin can be soothed by applying a moist cloth or bathing the affected area, and the water absorbed by the skin can subsequently be retained by using an occlusive substance. Because the evaporation of water on the skin's surface might dry up and irritate it, occlusive substances should be applied as away.(4)

b) Salt Baths

Spa treatments or taking a saltwater bath can both be considered forms of balneotherapy, or thermal mineral water therapy. The same theory suggests that taking a

hot spring bath can help people with atopic dermatitis.(4)

c) Coal Tar

Coal tar, a by-product of coal processing is used to treat skin symptoms like dryness, redness, flaking, scaling and itching. A clinical study involving the use of clinitar for four weeks to treat eczema, researchers found minimal difference in Clinitar's and 1% hydrocortisone cream's therapeutic efficacy. For scalp eczema, tar shampoos are additionally available. Tar products can be applied after applying a moisturiser. On occasion, applying tar to skin that is already irritated can make it worse.(5)

d) UV Phototherapy

Successful adjunct therapies for atopic dermatitis have included ultraviolet light. A study of narrow band UVB therapy (311 nm wavelength) revealed that the severity of atopic dermatitis might be reduced(6). Patients with atopic dermatitis had increased skin permeability solely in the lesional skin. Authors' analysis of skin permeability suggests that barrier dysfunction also contributes to the etiology of atopic dermatitis(7). The generation of superantigens by *S. aureus* are found to be suppressed by ultraviolet light. These superantigens have the capacity to stimulate T lymphocytes, which may in turn heighten the inflammatory response in atopic dermatitis sufferers. This could be a method by which UV radiation treats atopic dermatitis.

Topical steroids and emollients should be taken into consideration at the start of phototherapy to help prevent a potential flare-up. Additionally, UV can be used in conjunction with previously administered photosensitizing medications (psoralens), either orally or topically, to create the so-called psoralen plus ultraviolet-A radiation (PUVA) therapy (photochemotherapy).

e) Moisturizers

Xerosis is one of the primary clinical manifestations of AD. Topical moisturizers are applied topically to treat xerosis and prevent transepidermal water loss. Conventional moisturizers have different concentrations of emollient, occlusive, and/or humectant chemicals. Emollients (such as glycol and glyceryl stearate, soy sterols) lubricate and soften the skin, occlusive agents (such as petrolatum, dimethicone, mineral oil) create a layer to stop water evaporation, and humectants (such as glycerol, lactic acid, and urea) draw in and retain water. The severity of AD and inflammation can thus be somewhat reduced by moisturizers themselves. When treating moderate to severe illness, moisturizers should be a part of the regimen and can serve as the main treatment for mild illness. They are also a crucial part of flare prevention and maintenance therapy (8).

II. Topical Therapies :

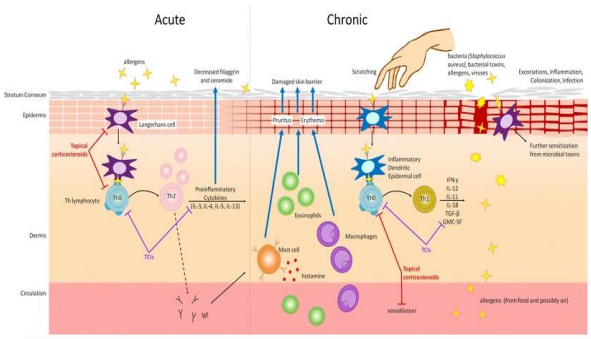
a) Corticosteroids

According to the skin condition (pruritus, insomnia, fresh flare), glucocorticosteroids are used as a first-line anti-inflammatory treatment for inflammatory skin. (9)

Mechanism of action : A glycoprotein known to be as lipocortin is stimulated by the corticosteroids. The resulting lipocortin prevents phospholipase A2 from releasing arachidonic acid from phospholipids. Corticosteroids, however blocks the mRNA that is necessary for the production of interleukin-1. Corticosteroid acts on interleukin-1 production and arachidonic acid metabolism resulting into anti-inflammatory, immunosuppressive response (10). Additionally, topical corticosteroids intervene directly at the DNA level to elevate the expression of anti-inflammatory genes and indirectly by inhibiting inflammatory transcription factors like Nuclear factor kappa B (NFkb) to decrease the expression of pro-inflammatory genes. (11)

b) Topical Calcineurin Inhibitors (TCI)

Macrolactams involving Tacrolimus and Pimecrolimus are thought to be have immunosuppressive properties. Both TCI’s are known to exert their immunosuppressive effects by inhibiting the activation of T lymphocytes, thereby decreasing the release of the various proinflammatory cytokines discussed previously (Fig. 2) TCI’s, in contrast to topical corticosteroids, have no impact on Langerhans cells and do not lessen the quantity of Th cells in healthy skin. Both TCIs have a lower transepidermal penetration (70–100 times less) than topical corticosteroids, with tacrolimus in ointment having a transepidermal flux that is roughly five times lower than pimecrolimus in cream(12). These qualities have led to tacrolimus and pimecrolimus being researched



for a variety of additional inflammatory skin conditions. (13). Tacrolimus has the potency that corresponds to a moderate to strong topical corticosteroid, whereas pimecrolimus has the potency of a mild corticosteroid cream. Topical calcineurin inhibitors do not have the negative effects of corticosteroids, such as skin thinning, which enables regular treatment for extended periods of time. Topical calcineurin inhibitors can also be use in the proactive treatment strategy (14).

Fig 2 : The mechanism of atopic dermatitis and sites of action of topical calcineurin inhibitors and topical corticosteroids.(15)

c) Topical Antihistamines and Antipruritic agents

Topical Diphenhydramine

Topical antihistamines are advised as an Over the counter (OTC) medication for the treatment of itching in AD. However, Caladryl's diphenhydramine component can be harmful if it is taken transdermally. In 8-years old boy mental confusion and hallucinations brought on by topical Caladryl and Benadryl spray have been reported. In addition, documented delayed hypersensitivity reaction. (16)

Doxepine

Patients with different types of eczematous dermatitis, such as lichen simplex chronicus, nummular eczema, or contact dermatitis, may get relief from their pruritus by using doxepine hydrochloride 5% cream (4). In a double-blind trial, patients with eczematous dermatitis who received 5% doxepin hydrochloride cream results into significantly less pruritus than those who received a vehicle alone. Despite years of research, the pathophysiology of the pruritus brought on by eczema is also yet unknown. Doxepin is a powerful H1 and H2 receptor antagonist. Based on in vitro findings, other histamine receptor antagonists including hydroxyzine(H1), diphenhydramine (H1), and cimetidine (H2) do not have affinity for both receptors as that of doxepine. (17)

1% Pramoxine Hydrochloride

Anesthetic topical Pramoxine has been used to treat wounds. In the open-label trial the results demonstrated the potency of a novel mixture of lactic acid 12% neutralised with ammonium hydroxide and pramoxine HCl 1% in hydrating and reducing the itching caused by dry skin. After the application of day 1, on day 3, there had been noticeable changes in the expert grader's assessment of skin dryness and skin surface hydration, which persisted over the course of the treatment until day 7. (18)

d) Topical Antibiotic

The high rate of Staphylococcus aureus cutaneous colonisation (up to 90% in moderate to severe eczema) in AD may be due to a multitude of abnormalities in innate cutaneous immunology (19). A successful management of AE includes anti-staphylococcal medication. Antibiotics can be used as a stand-alone therapy, as a component of a corticoid-steroid combination therapy either systemically or topically. Even when not actively infected, antibacterial medication reduces bacterial colonisation while also frequently improving AE. (20)

Fusidic acid or mupirocin can be applied topically to treat localised impetiginized eczema lesions satisfactorily (21), but other antibiotics like tetracyclines or polymyxins should not be applied topically (neomycin for the now-obsolete aminoglycoside). Despite the patient's resistance to methicillin or oxacillin, fusidic acid appears to be the preferred antibiotic due to its suppression of *staphylococci* at very low doses. (22)

Clinical studies have shown that mupirocin and fusidic acid are equally effective. (23, 24) In individuals with AE, there is very little chance of developing an allergic contact dermatitis to fusidic acid. Although topical neomycin has a high rate of resistance and is ineffective, it is rarely recommended due to frequent occurrence of allergic contact dermatitis (25, 26).

Mechanism of action of fusidic acid : FA facilitates the inhibition of protein synthess by hindering the turnover of elongation factor G (EF-G) from the ribosomes. By facilitating the full translocation of mRNA-tRNA in the final step of the peptidic-chain

elongation, the ribosomes interact with soluble EF-G during the synthesis of proteins. The next aminoacyl-tRNA freely bind to the aminoacyl site due to this mechanism. The interaction of EF-G and ribosomes is blocked when Fusidic acid binds to EF-G. (27)

e) Topical antiseptics :

For topical antibacterial treatment in patients with AD, antiseptics constitute an alternative to antibiotics. Antiseptics have the ability to develop resistance in *S. aureus* strains, which is one of their key benefits. Antiseptic baths can be quite helpful in cases of severe, widespread bacterial illness since they remove crusts and a significant portion of the bacterial load in doing so. Sodium hypochlorite, triclosan, chlorhexidine gluconate, and potassium permanganate are antiseptics used in baths. Since antiseptic baths cause the skin to become desiccated, it is crucial to keep bathing times to 5–10 minutes and moisturize the skin with emollients right away.

1. Triclosan: By inhibiting the enoyl-acyl carrier protein reductase (fabI), which is necessary for the production of fatty acids by bacteria, triclosan has an antibacterial effect. In dermatology, triclosan 1–2% is used as an antibacterial agent (28). An emollient containing triclosan was compared to an emollient alone (vehicle) in a randomised clinical research to see which was more effective and safe for treating AD in 60 participants. At day 14, there was a significant drop in SCORAD from baseline for the research cream compared to vehicle (P 0.05). Even though the mean reduction from baseline had improved by day 27, this was no longer significant (P > 0.05). Only four patients experienced minor side effects from the treatment. Patients participating in the trial applied a considerably smaller mean total amount of topical steroid than did the controls (P = 0.40). Patients found the leave-on emollient with triclosan to be safe and quite agreeable. (29).

2. Povidone iodine : Povidone iodine (PVP-I) is a combination of polyvinylpyrrolidone (povidone, PVP) and elemental iodine. The elemental iodine is gradually released from the complex and has a toxic effect on both eukaryotic and prokaryotic cells by iodizing lipids and oxidizing compounds in the cytoplasm and membranes (28).

   An investigation on the effectiveness of 10% povidone-iodine solution applied to atopic dermatitis patients was conducted using a case-control design. Prior to and during topical povidone-iodine treatment, *Staphylococcus aureus* density on eczematous lesions and the severity of the lesions were compared. After receiving povidone-iodine treatment, patients who have *S. aureus* colonised at a density of more than 1000 CFU/10 cm^2 found to have a 10-100-fold reduction in the amount of the bacteria. Patients colonised S. aureus at a density of greater than 1000 CFU/10 cm^2 experienced a reduction in erythema and exudation after receiving povidone-iodine therapy (30).

3. Octenidin : In order to disinfect skin and mucous membranes, octenidindihydrochlorid (0.1%) and phenoxyethanol (2%) are used in combination. Octenidin is appropriate for antiseptic dressings in locally infected eczema in AD patients. Octenidin exhibits strong antibacterial activity, effectiveness against MRSA, minimal toxicity, and good mucous membrane tolerance.

4. Sodium hypochloride (bleach): Since the 18th century, sodium hypochlorite (NaOCl), sometimes known as bleach, has been used as an antiseptic and disinfectant (31). Bleach can exist as hypochlorous acid (HOCl), a hypochlorite ion, or in its molecular form depending on the pH. Neutrophils naturally create hypochlorous acid, which functions as a potent oxidant and microbic agent. HOCl has only lately been utilised in commercial formulation since it is not shelf-stable (32).

Mechanism of action : For the treatment of AD, NaOCl has been used and debated quite a bit because it is well-tolerated, widely available, and known to reduce *staphylococcal* colonisation and AD severity (32). *S.aureus*, particularly methicillin-resistant *S. aureus*, has been demonstrated to be resistant to NaOCl both in vitro and in vivo.

HOCl and sodium hydroxide are produced when NaOCl is combined with water (NaOH). *S. aureus*, common bacteria, fungi, and viruses are all wiped out by hypochlorous acid non-selectively . Bleach appears to affect AD through a number of additional key

mechanisms in addition to the eradication of microorganisms. These additional mechanisms include: reduces Interleukin-12 response and thus preventing the shifting of T helper cells type -2 and T helper cells type -1 and AD chronicity, decreasing IgE production by B cells, decreasing mast cell activation and histamine release, and downregulating Mitogen activated protein kinase (MAPK) and Nuclear factor kappa B (NF-KB) pathways, which results in a reduction in the production of proinflammatory cytokines and pruritogenic cytokines (TSLP), Along with this, it lessens the dorsal root ganglia's intracellular calcium concentration, which reduces the neurosensory transmission of pruritic stimuli. (33).

III. Systemic Therapies:

a) Oral antibiotics

Acute exacerbations caused by *S. aureus* infection can be treated by systemic antibiotic treatment (34). The newer macrolide antibiotics (azithromycin, clarithromycin, and roxithromycin), and erythromycin have become the antibacterial agent of choice for treating generalised impetiginized AE. First-generation cephalosporins and penicillinase-resistant penicillin (dicloxacillin, oxacillin, flucloxacillin, or cloxacillin) should be used to treat macrolide-resistant *S. aureus* (25, 26).

Mechanism of action: Antibiotics with an inhibitory effect on protein synthesis can suppress the production of superantigens. Moreover, one of the study demonstrated that replication of DNA coding of superantigen produced by S. aureus was suppressed only by roxithromycin (ROX), which is a new macrolide. This finding suggests that ROX may have an effect at the gene level. These results suggested that the suppressive effects of antimicrobial agents that act as inhibitors of protein synthesis on superantigen production from S. aureus may be useful in the treatment of atopic dermatitis. (35).

b) Oral Immunesuppresants

cyclosporin-a (Cyc-a)

A major target of the immunomodulator cyclosporin are T lymphocytes. It suppresses cytokine transcription by interacting with intracellular cyclophilin(36). There were 15 patients (9 men and 6 women) in one of the case-control studies. They were all severely ill after undergoing treatment for an average of 6 months at a mean starting dose of 2.8 mg/kg/day and a mean maximal dose of 3.3 mg/kg/day of cyclosporin. Within the first two weeks, there was an improvement, and it took an average of 10 weeks to achieve the maximum benefit. In 73% of patients, the condition had progressed from severe to none, mild, or moderate by the end of treatment. Three of the five patients who experienced an eczema flare while receiving therapy had their medication dose reduced (37).

Methotrexate

For both children and adults with AD, methotrexate is a possible off-label treatment. Methotrexate (MTX) is a synthetic chemical analogue of folic acid which acts as an anti-metabolite for the treatment for atopic eczema. In a clinical study twenty adult atopic dermatitis patients who had failed to respond to traditional therapies were given a dose of methotrexate every week ranging from 7.5 to 25 mg (33). Three months of methotrexate use served as the endpoint for the doctor's overall evaluation. After three months of treatment, 75% of patients showed improvement in their eczema, with responses appearing between four and eight weeks later. The medication did have some serious adverse effects, though, like nausea and increased liver enzyme levels.(38)

Mechanism of action: Systemic sclerosis, morphea, lupus erythematosus, dermatomyositis, and crusted scabies have all been treated with methotrexate (MTX), a folic acid analogue with anti proliferative (anti neoplastic, cytotoxic), immunosuppressive, and anti-inflammatory properties. Dihydrofolate reductase, which is required for the synthesis of pyrimidine and purine nucleotides, is thought to have a role in the inhibition of cell proliferation by preventing DNA/RNA synthesis(39).

Azathioprine

Azathioprine is used as a steroid-sparing drug, a monotherapy, or for its immunosuppressive characteristics. Studies have shown that azathioprine's anti-proliferative properties cause a general reduction in the severity of AD. (40)

A randomised, controlled, 6-month crossover clinical trial was performed in 37 patients with age group of 17 to 73 years to demonstrate the efficacy of

azathioprine. In a crossover design, azathioprine (2.5 mg/kg bw/day) or placebo were administered for three months. In comparison to the placebo group, the azathioprine group experienced a 26% reduction in the SASSAD skin severity score (P 0.01). Significant improvements in pruritus, lack of sleep, and exhaustion were seen while taking azathioprine but not when taking a placebo. (41)

Mechanism of action: Azathioprine is quickly transformed in the liver to 6-mercaptopurine (6-MP), which is an active metabolite. Purine production is predominantly inhibited, which thus prevents cell division. It is a purine analogue that transforms into 6-mercaptopurine when metabolised, 6-MP is then further metabolized into active compounds, including 6-thioguanine nucleotides (6-TGN), which have immunosuppressive properties by preventing DNA synthesis. (42)

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a morpholinoester of mycophenolic acid (MPA) (43).An additional pilot research revealed that mycophenolate mofetil was typically well-tolerated and efficient in treating severe atopic dermatitis. In this trial, mycophenolate mofetil treatment resulted in a 74% improvement in atopic dermatitis severity as determined by the subjective SCORAD score (44).

Mechanism of action:

Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA), an inhibitor of inosine-5'-monophosphate dehydrogenase, which preferentially depletes guanosine nucleotides in T and B lymphocytes and inhibits their proliferation, stifling cell-mediated immune responses and antibody production.

c) Oral Glucocorticoids

Glucocorticosteroids are a first-line anti-inflammatory treatment, applied on inflammatory skin according to the needs (pruritus, sleeplessness, new flare). (9)

Mechanism of action : It is well known that corticosteroids promote the synthesis of the lipocortin glycoprotein. The resulting lipocortin prevents phospholipase A2 from releasing arachidonic acid (the building block of prostanoids and leukotrienes) from phospholipids. Corticosteroids, however, block the mRNA necessary for the production of interleukin-1. Corticosteroids' acts on the production of interleukin-1 and the metabolism of arachidonic acid result in anti-inflammatory and immunosuppressive effects(10). Aside from indirectly inhibiting pro-inflammatory transcription factors like NFkb, topical corticosteroids also act directly at the DNA level to increase the expression of anti-inflammatory genes and decrease the expression of pro-inflammatory genes. (11)

d) Biologic therapies

Dupilumab (dup)

A completely human monoclonal antibody called DUP blocks the common alpha chain receptors IL-4 and IL-13. As a first-line therapy for moderate-severe adult AD, it is the first biologic medication to receive this approval. When topical medications are insufficiently successful and when systemic therapy are not advised, Dup is suggested as a disease-modifying medication for adult patients with moderate to severe AD. DUP treatment may be coupled with the use of topical emollients on a daily basis and topical anti-inflammatory medicines (TCS, TCI) as necessary.(45)

Nemolizumab

Nemolizumab, an anti-IL-31 receptor A medication, showed excellent efficacy in reducing itching in AD patients(45). A long-term, double-blind, randomised, trail was performed to examined the effectiveness and tolerability of nemolizumab for the treatment of AD patients whose condition was not effectively controlled by topical medication. The research showed that benefits in pruritus, dermatitis, and sleep parameters compared to placebo in the 12-week placebo-controlled part of the study were sustained or gradually increased with long-term treatment for up to 64 weeks(46).

Other biologics including ustekinumab (anti-IL-12/23) and rituximab (anti-CD20), mepolizumab (anti-IL-5), omalizumab (anti-IgE), and mepolizumab (anti-IL-5), are currently not advised for AD.

e) Other therapies

1. Phytotherapies

Cardiospermum

The active ingredient in the cardiospermum is found in the plant's flowering aerial portions, which exhibit a significant cortisone-like effect and are beneficial for treating itching and inflammatory skin allergies. To treat inflammatory dermatitis, hives, eczema, and

insect bites, Cardiospermum formulations are now in use. Phytosterols, which also include anti-inflammatory, moisturizing, sebum-regulating, anti-pruriginous, and actions that reduce skin redness and prevent flaking, are the active elements that give off the cortisone-like effect(47). The inclusion of phytosterols in cardiospermum have an affinity for lipids in the epidermis and cell membranes, which helps to exhibit its cortisone-like anti-inflammatory activity by activating phospholipase A2 while maintaining the stability of cell membranes. In one of the clinical case studies, data show that regardless of the associated treatment, a 15-day course of C. halicacabum leads to an improvement in the conditions in subjects with dermatitis of varying degrees. (48)

Evening Primrose Oil

Gamma linolenic acid (GLA) is an essential omega-6 fatty acid found in seeds of evening primerose flower that is also a component of the lipids that make up the skin barrier. Topical application of GLA can thus directly restore the structure and function of the skin barrier while also reducing skin inflammation.

Patients with atopic eczema may benefit from using evening primrose oil to treat their condition because of the correlation between low levels of essential fatty acids and low levels of linoleic acid's delta-6-desaturase metabolites. In a double-blind, placebo-controlled, parallel group research, 58 of 60 kids with atopic dermatitis who required ongoing topical steroid treatment underwent a 16-week treatment term with either Epogam evening primrose oil or placebo capsules. Although there was no discernible difference between the placebo and Epogam groups, the study showed a considerable improvement in eczema symptoms.(49)

Milk Thistle (Silybum marianum)

The seeds of the plant *S. marianum* are the source of the polyphenolic flavonoid known as silymarin. Silymarin possesses an anti-inflammatory property through NF- kB inhibition. Silymarin, which has a large number of pro-inflammatory cytokines, chemokines, and enzymes, decreases the expression of T helper 1 (Th1) and raises the expression of Th2, balances the inflammatory factors IL-1 and IL-6. In a randomised double-blind controlled clinical trial, Mometasone 0.1% or a herbal cream containing Silymarin and Fumaria Officinalis were given at random to 40 patients with mild to moderate eczema. The course of treatment lasted for two weeks, and the patients were assessed before and after two weeks of treatment using the SCORAD system. In a mometasone group, the mean SCORAD score was 27.665.9 before therapy and 4.771.6 after therapy; in a herbal group, the mean SCORAD score was 26.057.1 before therapy and 6.9442.6 after therapy. The study concluded that these plants may be a new treatment for eczema symptoms and problems that are related to them. (50)

2. Eczema and Probiotics

The microbiome is essential for the growth and homeostasis of the immune system. Recently, modifications in immunological responses and the emergence of skin illnesses like atopic dermatitis have been related to changes in microbial composition and function, or dysbiosis, in the skin and gut.

Probiotics are preparations that contain microorganisms or parts of them. Probiotics may offer extra defence against atopic dermatitis in young children when given concurrently with breastfeeding. The preventive effectiveness of probiotics over a placebo was examined in this investigation, which was part of a double-blinded, placebo-controlled trial. A study of 62 breast-feeding mother-infant pairs found that probiotics significantly reduced the risk of atopic eczema in infants during the first two years of life compared to placebo (15% and 47%, respectively). Probiotics have been shown to reduce allergic inflammation associated with atopic eczema, in part because they increase the production of TGF- in breast milk (51).

3. Chinese herbal therapy

Chinese herbal remedies are component of traditional Chinese medicine, which also includes acupuncture, diet, and exercise in addition to Chinese herbs applied topically or orally. 37 children and 31 adults were given either an active or a placebo plant mixture over an 8-week period in a crossover study with a comparable design. Erythema, surface damage, and percentage of afflicted region were considered when determining severity. In the children's group, the median percentage change for surface damage was 63.1% for Chinese herbs and 6.2% for a placebo. The 23 youngsters who choose to continue taking Chinese

herbs exhibited overall better outcomes than those who stopped this therapy in a 1-year follow-up. In the adult group, the geometric mean for surface damage at the end of the Chinese herb treatment was 11.3 against 111 at the end of the placebo. 121 After one year. 12 of the 17 people who choose to continue the herbal treatment had a clinical score reduction of more than 90%, which was significantly better than the clinical scores of the 11 patients who opted not to continue taking the medication. (52)

III. CONCLUSION

The management of atopic dermatitis (AD) requires a multifaceted approach that includes various therapeutic options. While basic therapy focusing on moisturization and avoidance of triggers forms the foundation, topical glucocorticoids and topical calcineurin inhibitors (TCIs) are commonly used for exacerbation management. Proactive treatment methods, such as intermittent or daily applications of TCIs or low-potency steroids, have shown promise in preventing future flares. In cases where conservative measures and topical treatments are insufficient, systemic immune-suppressive therapy can be considered for extreme refractory instances of AD. Additionally, superinfection and microbial colonization may necessitate antimicrobial therapy as a complementary approach. Adjuvant therapies, such as exposure to UV light (preferably UVA1 or UVB 311 nm), have demonstrated positive outcomes in some patients. Moreover, targeted biologics are emerging as promising options for the management of AD. Beyond conventional treatments, other alternative therapies have also been explored. Phytotherapies like Cardiospermum, Evening Primrose Oil, and Milk Thistle (Silybum marianum), as well as Chinese herbal therapy and probiotics, have shown potential in alleviating AD symptoms. However, more research is needed to establish their efficacy and safety profiles. Overall, the evolving treatment landscape for AD provides clinicians with a range of options to tailor therapy based on individual patient characteristics and needs. Ongoing research and advancements in the field are expected to further enhance our understanding and management of this chronic inflammatory skin condition.

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