A SYSTEMIC REVIEW ON MEDICAL TREATMENT OF ATOPIC DERMATITIS (ECZEMA)

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Abstract: -

Atopic dermatitis (AD) is a chronic, inflammatory skin disorder characterized by intense itching, erythema, and dry skin. It commonly affects children but can persist into or appear in adulthood, significantly impacting the quality of life. Effective management of AD is essential to alleviate symptoms, reduce flare-ups, and improve the patient's overall well-being. This systematic review aims to evaluate the effectiveness, safety, and recent advancements in the medical treatment of AD. A comprehensive literature search was conducted across major databases, including PubMed, Cochrane Library, and Embase, from inception to 2023. Studies included randomized controlled trials, cohort studies, and meta-analyses focusing on various medical treatments for AD. Primary outcomes assessed were clinical efficacy, safety profile, and impact on quality of life. A total of 75 studies were included, covering various treatment modalities such as topical corticosteroids (TCS), calcineurin inhibitors, biologics, systemic immunosuppressants, and newer agents like Janus kinase (JAK) inhibitors.

Topical treatments, including TCS and calcineurin inhibitors (e.g., tacrolimus, pimecrolimus), remain the cornerstone for mild to moderate AD. TCS are effective in reducing inflammation and controlling flare-ups but can cause skin atrophy and hypothalamic-pituitary-adrenal (HPA) axis suppression with prolonged use. Calcineurin inhibitors serve as alternatives, particularly for sensitive skin areas, offering similar efficacy with a lower risk of skin thinning but with a higher incidence of local irritation. For moderate to severe cases, systemic immunosuppressants such as cyclosporine, methotrexate, and azathioprine are commonly used. Although effective, these agents have significant side effects, including nephrotoxicity, hepatotoxicity, and bone marrow suppression, necessitating careful monitoring. Biologics, particularly dupilumab, have revolutionized the treatment landscape for moderate to severe AD. As an interleukin-4 receptor alpha antagonist, dupilumab has demonstrated significant efficacy in reducing disease severity and pruritus, with a favorable safety profile primarily limited to conjunctivitis and injection site reactions. JAK inhibitors, such as upadacitinib and abrocitinib, represent a novel class of oral medications that have shown rapid and significant improvements in symptom control compared to placebo, providing a promising alternative for patients unresponsive to conventional therapies. However, their long-term safety remains a concern, with potential risks including infections, thromboembolic events, and cardiovascular issues.

Other treatments like antihistamines, though commonly used, show limited efficacy in pruritus control. Emerging therapies, including phosphodiesterase-4 inhibitors and microbiome-modulating treatments, are under investigation and show potential for future management strategies. The management of AD has evolved significantly, with biologics and JAK inhibitors offering new options for patients with moderate to severe disease unresponsive to traditional treatments. However, safety concerns necessitate a careful, individualized approach to therapy. Future research should focus on long-term safety data, optimizing treatment combinations, and exploring novel pathways to improve patient outcomes further

Keywords:- Atopic dermatitis, topical corticosteroids, biologics, JAK inhibitors, systemic immunosuppressants, systematic review

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Introduction: -

Eczema or known as atopic dermatitis, skin disorder or a condition that causes swelling, scaling, oozing/weeping, and dryness [1]

It is an ongoing inflammatory skin condition that has affected more than two hundred million people worldwide, including 20% of children and 10% of adults.[14]

AD has a long history. It was first described in 1892 by Besnier who named it "prurigo diathesique". It shows an association between skin inflammation and genetic constitution, in 1927 Brocq suggested the term "Constitutional Eczema". Wise and Sulzberger 1933 changed this name to "Atopic Dermatitis", finally adopted by Hanifin and Rajka in 1980. This is the current denomination adopted in the USA, while in Europe the most common definition is atopic eczema. Since eczema in atopic patients may be linked to or a sign of the onset of certain allergic diseases like rhinitis and asthma, the World Allergy Organization (WAO) Committee proposed in 2004 to refer to any inflammatory condition determined by an IgE reaction as "Atopic Eczema."[3]

The pathophysiology of AD is intricate and multifaceted. Genetic factors include structural proteins in the stratum corneum that code for gene deficiencies, like filaggrin. Genes encoding Th2 cytokines, like IL-4 and IL-13, are upregulated, and gene variants encoding their receptors are also implicated. Skin barrier dysfunction is associated with overexpression of the Th2 axis and downregulation of important proteins that maintain the stratum corneum, including filaggrin, loricrin, involucrin, and corneodesmosin. Superinfection by S. aureus bacteria is more likely when the LL-37 and other antibacterial peptides defensin are produced at a reduced level. Furthermore, several environmental factors are linked, including humidity, truck pollution, and skin irritants.[23]

The development of secondary skin infections with Staphylococcus, Streptococcus, and herpes species, chronic post-inflammatory skin changes, scarring from picking and scratching, and severe morbidity from sleep disturbances may all be avoided with early identification and treatment.[9]

Epidemiology: -

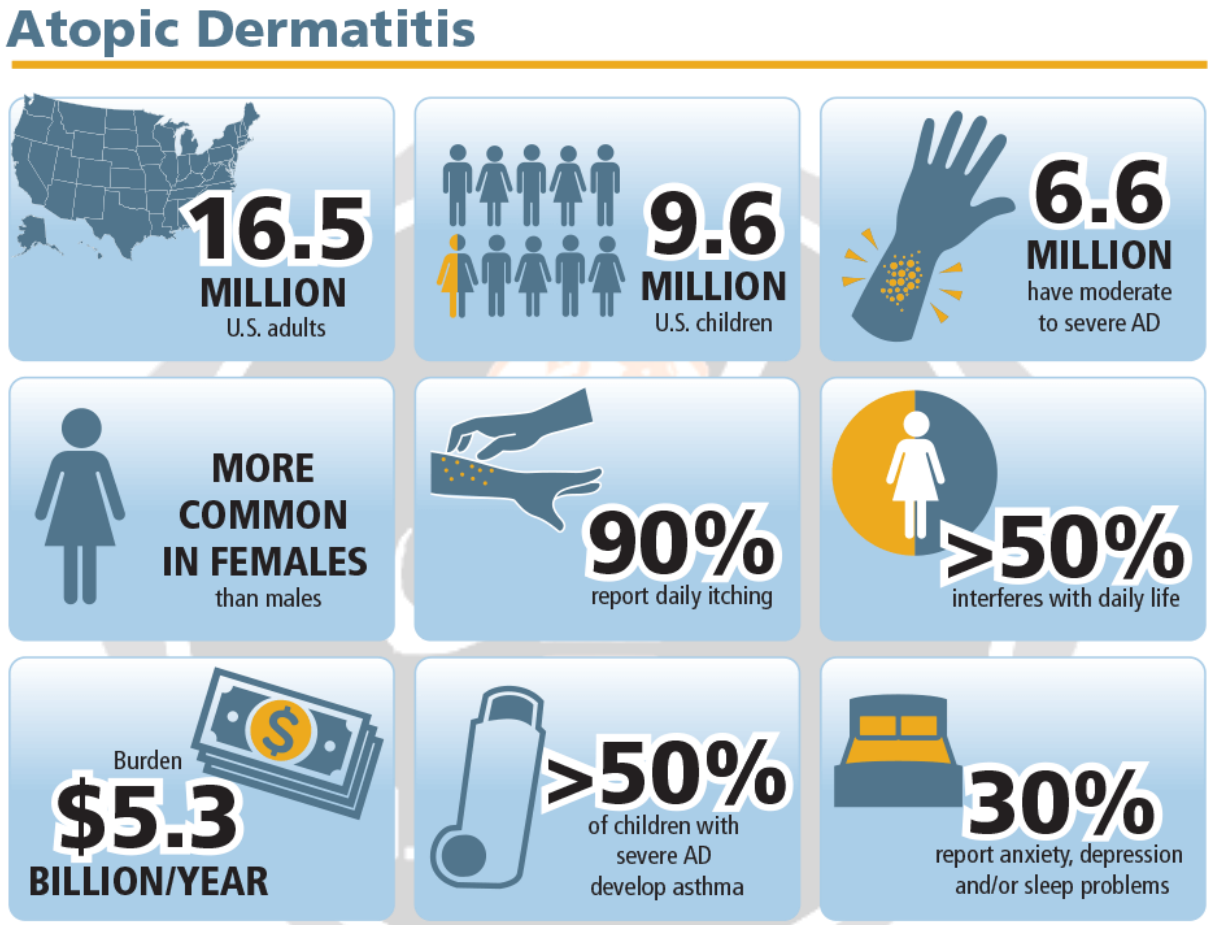
According to data from the WHO Global Burden of Diseases research, AD is the leading source of non-fatal sickness burden among skin disorders, affecting at least 230 million people worldwide.[19] In babies, 15-20% of children, and 5–10% of adults have atopic dermatitis. It frequently begins in early childhood (60 percent of patients experience it in the first year of life, and 85% by the age of five), and 40–70% of patients have it resolved by adolescence. According to a recent Australian study that used longitudinal latent class analysis, approximately 25% of those suffering from atopic dermatitis continue to have symptoms throughout adulthood.[17]

The condition first manifests in adulthood in about 25% of afflicted persons. The quality of life is significantly impacted by atopic dermatitis not just for afflicted individuals but also for family members and caregivers. Numerous comorbid conditions exist in addition to disfigurement, itching, skin pain, and recurrent infections. These include obesity, growth and developmental impairment, respiratory, food, and gut allergies, chronic sleep deprivation, mental health and behavioral issues, and complications of social withdrawal.1,3 Compared to type 1 diabetes, moderate to severe atopic dermatitis has a higher psychosocial impact.7. Financial strains on individuals and society are also significant.[14]

The so-called "atopic march," which is defined by a regular sequence of atopic diseases preceding the development of additional allergic disorders later in adulthood, is frequently initiated by AD. Additional atopic

diseases that may follow include allergic rhinitis, asthma, and food allergies. The underlying characteristics of the disease determine how many individuals will acquire asthma and/or allergic rhinitis; data indicates that 50% of AD sufferers

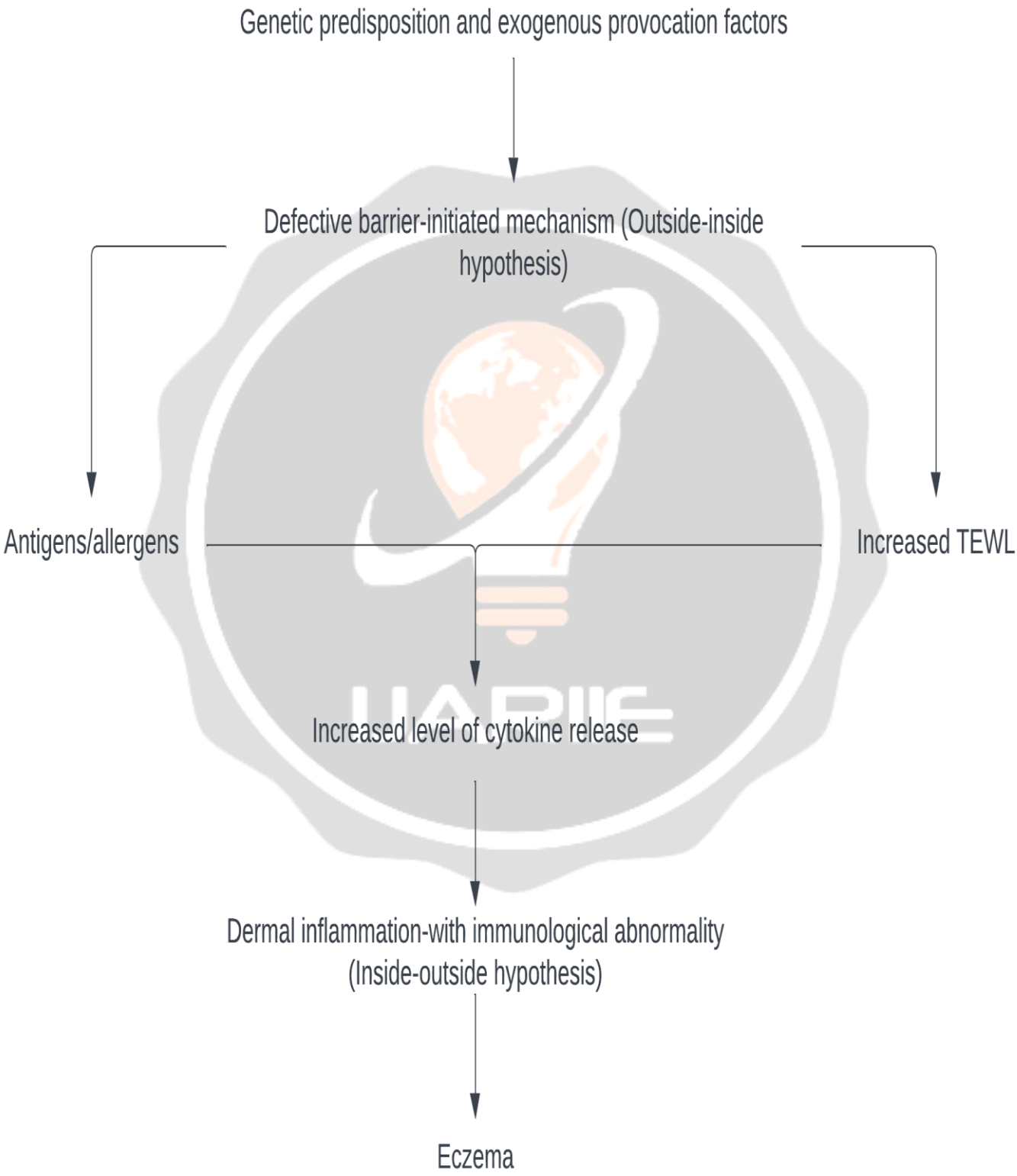
who begin before the age of two will go on to develop asthma in the years that follow. Additionally, AD kids who experience Inhalation allergies and asthma are more prone to experience serious illness. A worldwide cross-sectional web-based study conducted in the US, Canada, France, Germany, Italy, Spain, the UK, and Japan found that there was geographical variation in the prevalence of adult AD within each nation. The point prevalence of adult AD in the general population among participants by region was 2.1% in Japan, 4.4% in the EU, 3.5% in the US, and 4.9% in the EU. Region and scale have an impact on severity. On the other hand, fewer participants reported severe illness than mild or moderate illness.[21]

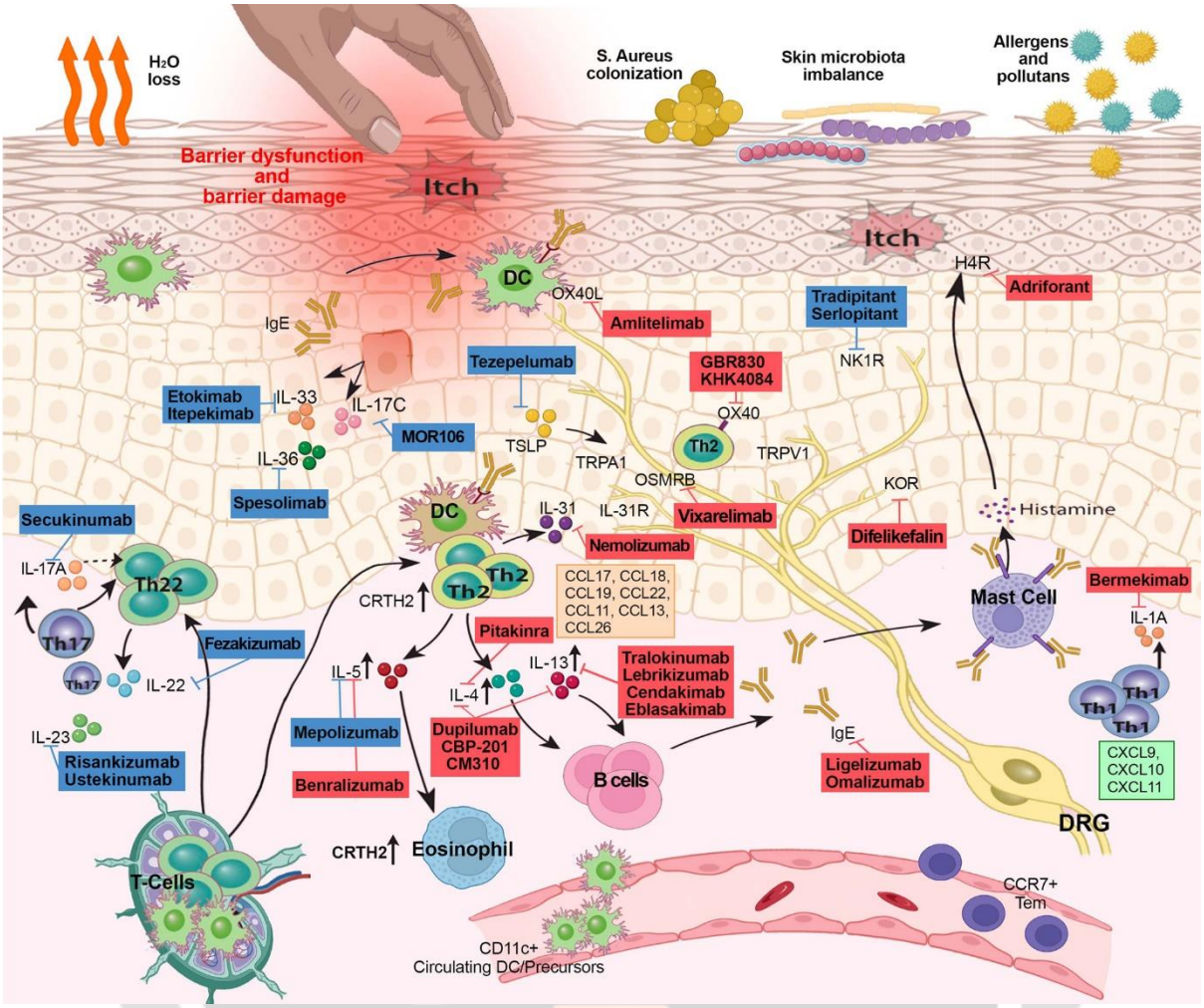


Etiology

Epidermal and immunologic protein-encoding genes have been linked to atopic dermatitis. The presence of a loss-of-function mutation in the gene encoding the filaggrin protein is a significant risk factor for atopic dermatitis in many patients. One of the constituents of the cornified cell membrane that results after keratinocyte differentiation is filaggrin. Building the stratum corneum's hygroscopic barrier—also known as the natural moisturizing factor—is ultimately dependent on it. 10% of people in Europe are heterozygous carriers of mutations causing filaggrin to lose function. These mutations raise the risk of more severe atopic dermatitis and elevated IgE levels, along with more intragenic copy mutations. Even without atopic dermatitis, filaggrin mutations are linked to asthma and peanut allergy.[9]

Pathophysiology





Clinical features and diagnosis: -

Three clinical phases can be present in atopic dermatitis. A crusting, weeping, vesicular eruption is the initial sign of acute atopic dermatitis (Figure 1). erythematous, scaly, dry papules and plaques are the first signs of subacute atopic dermatitis (Figure 2).[20]

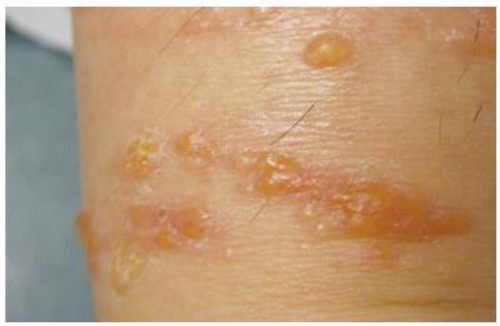


Fig.1 Acute atopic dermatitis in its sobbing, blistering form

Fig.2 Atopic dermatitis subacute in its dry, papular, scaly form.

Lichenification from recurrent scratching is a sign of chronic atopic dermatitis (Figures 3 and 4). Pityriasis alba is a more subdued manifestation of atopic dermatitis that frequently affects youngsters. It is distinguished by finely scaled, hypopigmented plaques that are weakly defined. Atopic dermatitis typically affects the face, forehead, wrists, hands, dorsal surfaces of the foot, eyelids, anterior and lateral necks, and body's flexural surfaces. The symptoms of atopic dermatitis include wide range of symptoms, making a differential diagnosis difficult.[18]

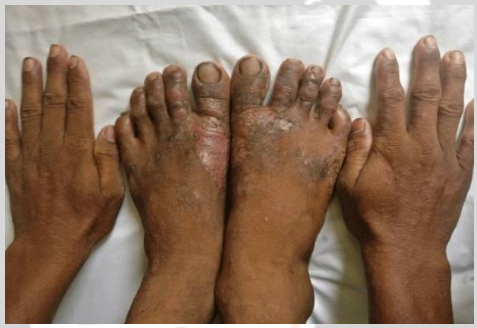


Fig. 3 Chronic atopic dermatitis demonstrating a lichenified plaque, as well as depigmentation resulting from repeated scratching.

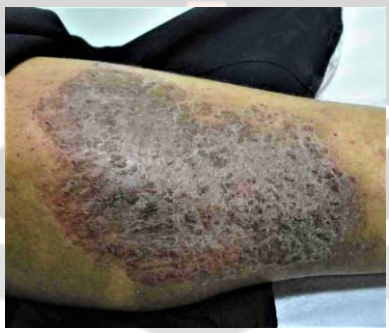


Fig.4 Chronic atopic dermatitis in its lichenified form. Note the associated hyperpigmentation

Except for newborns, toddlers, and the elderly, who often exhibit more unusual clinical symptoms, clinical diagnosis is typically straightforward. Skin biopsies can be employed to exclude malignant conditions such as cutaneous T-cell lymphoma, other common diseases that mimic, coexist with, or exacerbate AD, and, especially in pediatric cases, other uncommon conditions like primary immunodeficiencies and nutritional deficiencies.[25]

Many sets of criteria have been developed over time to support diagnosis, but the original Hanifin and Rajka criteria are still the most commonly utilized globally. Both the American Academy of Dermatology Consensus Criteria and the Hanifin and Rajka Criteria help identify the "essential, common, and associated features" of AD and can be helpful in a therapeutic setting.[5]

As a result, severe itching, atopic, subacute, or persistent eczematous lesions, as well as a persistent or recurrent illness course are the key characteristics. Any area of the body can get AD lesions, albeit they usually exhibit an age-related distribution pattern. Acute skin lesions that are widely spaced and exhibit significant erythema,

edema, excoriations, and serous effusion that appears as seeping or crusting are common in infants; these lesions are typically discovered on the cheeks, face, and trunk, sparing the diaper area.[17]

When AD affects flexor surfaces often, it grows more regional and chronic in children, exhibiting paler erythema, xerosis, and thicker skin due to repeated scratching. Adults and adolescents may experience isolated lesions, which usually affect the flexures, hands, and eyelids, in addition to a dispersed AD pattern. Adults may only exhibit persistent hand AD or the AD subtype that affects the head and neck, encompassing the scalp, shoulders, and upper trunk.[9]

Atopic Dermatitis Treatment: -

1. Supportive care (including counseling on appropriate skin care and avoidance of precipitating factors)
2. Antipruritic
3. Topical corticosteroids
4. Topical calcineurin inhibitors
5. Topical Carisbrooke
6. Topical Janus kinase BAK) inhibitor (e.g., ruxolitinib)
7. Phototherapy, particularly narrow-band ultraviolet B
8. Systemic immunosuppressants
9. Systemic biologic agents

The best way to treat atopic dermatitis is to take care of the underlying pathophysiologic mechanisms. Patients who get counseling on proper skin care and avoiding triggers are more able to address the underlying skin barrier problem. It is normal for scratching irritating lesions to aggravate them worse and cause further scratching. This scratch-itch cycle must be broken. phototherapy, topical immunosuppressants, and, if required, systemic immunosuppressants can all help reduce inflammatory flare-ups. Patients with erythroderma or severe superinfections may require hospitalization, but the majority of those When dealing with atopic dermatitis, are managed as outpatients.[12]

- Supportive care

The main targets of general skincare should be the most frequent causes of skin irritation, which include harsh soaps and excessive washing:
• Reducing the amount of time and frequency that you wash and bathe (showers and baths should only be taken once a day; you can replace a full bath with a sponge bath).
• Setting the bathing water's temperature to lukewarm after showering or bathing, pat dry your skin instead of rubbing it excessively. • Use moisturizers (ointments or creams; those with ceramide are especially helpful).
• Taking a bath with diluted bleach for superinfection of the skin (e.g., yellowish crusting suggesting impetigo).[13]

- Because they are sedatives, oral antihistamines can help reduce pruritus. Diphenhydramine (e.g., 25 to 50 mg), preferably in the evening to prevent the sedative effects during the day, and hydroxyzine (25 mg) three or four times a day (for children, 0.5 mg/kg every six hours or 2 mg/kg in a single nighttime dose) are options. Antihistamines that are non-sedating or low-sedating, including cetirizine (5 to 1 0 mg once a day), fexofenadine (60 mg twice a day or 180 mg once a day), or loratadine (10 mg once a day), may be helpful, but their effectiveness is unknown.

Doxepin, a tricyclic antidepressant that similarly blocks H1 and H2 receptors, may also be helpful; however, it is not advised for children under the age of 12 to take 25 to 50 mg before bed.
Reducing emotional tension is beneficial and aids in ending the cycle of itching and scratching. Stress can have an impact on the patient (e.g., being unable to sleep due to itching) as well as the family (e.g., being kept up by a crying baby). Dietary adjustments meant to prevent exposure to allergic foods are typically pointless, inefficient, and cause needless stress. Food allergies are a fairly infrequent cause of atopic dermatitis. To reduce excoriations and subsequent infections, fingernails should be kept short.[22]

- Topical corticosteroids

Patients with severe atopic dermatitis that is resistant to treatment should be the only ones prescribed systemic corticosteroids. Atopic dermatitis lesions can be improved by oral corticosteroids, however stopping these drugs may cause the condition to flare up again. Rebound impact risk can be reduced when using a systemic corticosteroid to treat a significant flare-up of atopic dermatitis by decreasing the medication while increasing topical corticosteroid treatment and heavily moisturizing the skin. Patients with atopic dermatitis benefit from topical corticosteroids, although frequent moisturizer use shouldn't be substituted for these medications. Topical steroids have well-known systemic and local side effects. Skin atrophy, striae, telangiectasias, hypopigmentation, rosacea, perioral dermatitis, and acne are examples of local consequences. Glaucoma, cataracts, and adrenal suppression are examples of systemic side effects.

Although systemic corticosteroids often offer effective emergency relief, prolonged usage of these drugs should be avoided due to their numerous negative side effects. Other treatments are usually needed to manage the tapering and termination of systemic corticosteroids because atopic dermatitis tends to flare when these medications are withdrawn.[21]

- Topical calcineurin inhibitors

Cincalcineurin inhibitors include topical tacrolimus and pimecrolimus. These T-cell inhibitors are indicated for mild to severe atopic dermatitis or in cases where the side effects of corticosteroids are a concern. Two applications of tacrolimus ointment or pimecrolimus cream are made each day. After application, burning or stinging is often momentary and goes away in a few days. Fewer people flush.

- Topical crisaborole

Topical phosphodiesterase-4 inhibitors include crisaborole. Patients two years of age or older with mild to moderate atopic dermatitis can benefit from using 2% ointment of crizaborole. Two times a day, crisaborole is applied to eczema-affected regions. Using it on mucous membranes is prohibited. The most frequent side effect following application is burning or stinging.[18]

- Topical ruxolitinib

An inhibitor of Janus kinase BAK) is rufolitinib. When other topical prescription therapies are either ineffective or not recommended for immunocompetent patients aged one to two years old, roxolitinib 1.5% cream may be used as a short-term, noncontinuous treatment for mild to moderate atopic dermatitis. For a maximum of eight weeks, rufolitinib is administered topically twice a day, covering up to twenty percent of the body's surface area.[8]

- Phototherapy

For severe cases of atopic dermatitis, phototherapy with narrow-band ultraviolet B (UVB) is beneficial, especially when topical medications and proper skin care are ineffective at controlling inflammation. Nowadays, psoralen with UVA (PUVA) therapy is rarely utilized because narrow-band UVB is significantly more effective than the previously employed broad-band UVB. Although phototherapy with narrow-band UVB has not been demonstrated to raise the incidence of skin cancer, this is still a worry, especially when used on youngsters or for prolonged periods. When topical treatments and proper skin care fail, this danger must be compared to the risks of additional systemic treatments.

Home phototherapy is a good substitute for office-based phototherapy if it is too inconvenient or not available. Several phototherapy systems for home usage come with programmable capabilities that let medical professionals control and monitor a patient's use of the equipment.

If phototherapy is not an option, exposure to the sun naturally can serve as a substitute. Serious infections, demise, cancer, heart attacks, and thrombosis are among the risks.[7]

- Systemic biologic agents

There are now two biologics (targeted systemic immunosuppressants) available to treat moderate to severe atopic dermatitis.

A completely human monoclonal IgG4 antibody called dupilumab prevents proinflammatory Th2 cytokines like IL-4 and IL-13 from signaling in atopic dermatitis. It is suggested for individuals whose illness is not sufficiently controlled with conventional treatments and is offered for addressing atopic dermatitis ranging from moderate to severe in individuals aged six and above.

Subcutaneous dupilumab administration involves a loading dosage of 600 mg, which is followed by 300 mg every two weeks; patients under 60 kg are given a 400 mg loading dose, which is followed by 200 mg every other week. Injection site responses, conjunctivitis, blepharitis, keratitis, ocular pruritus, oral herpes, and other herpes are the most frequent side effects. eosinophilia, simplex viral infections, and dry eyes.

A completely human monoclonal antibody called trasokinumab-ldrm targets the IL-13 receptors alpha 1 and alpha 2. It can be used to treat people with moderate-to-severe atopic dermatitis whose condition is not sufficiently controlled by topical treatments.

Subcutaneous injections of 600 mg of talokinumab-ldrm are administered, with a maintenance dose of 300 mg every other week. The most frequent side effects include eosinophils, injection site reactions, conjunctivitis, and upper respiratory infections.[10]

- Systemic immunosuppressants

T-cell function is inhibited by systemic immunosuppressants such as azathioprine, methotrexate, mycophenolate, and cyclosporine. When topical therapy and phototherapy are ineffective in treating extensive, resistant, or incapacitating atopic dermatitis, these drugs may be prescribed. The potential for side effects must be weighed against its use, especially when used over an extended period. The newest systemic immunosuppressants, upadacitinib, and abrocitinib, are indicated for managing moderate to severe atopic dermatitis in individuals aged 12 and above when other systemic medications, such as biologic agents, are not effective in controlling the disease or when using those therapies is not recommended. BAK 1 is inhibited by both.[16]

Conclusion

AD is one of the most prevalent diseases worldwide and is associated with a very burdensome impact on healthcare resources and patients' and caregivers' QoL. Moreover, AD is associated with numerous medical and mental health comorbidities, with important implications for its management and treatment. Considering there is also increasing evidence that AD may progress to other allergic phenotypes, a clear need to improve disease prevention arises. At the moment, patients with atopic dermatitis are experiencing favorable conditions as numerous medications have been authorized for treating the condition, with additional ones being researched. Oral JAK inhibitors have the potential to revolutionize treatment for patients with moderate-severe AD. It is crucial to establish treatment objectives that enhance efforts to achieve alignment of treatment approaches. A multi-faceted approach is required..

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