International Journal of Research and Review
Vol.7; Issue: 6; June 2020
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Atopic Dermatitis: A Review on Diagnosis and Management

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ABSTRACT

Atopic Dermatitis (AD), also known as eczema, is a chronic, relapsing, and itchy inflammatory skin condition. The pathogenesis of AD including genetic, environmental, and immunologic factors. The primary biologic changes in AD are decreased skin barrier function, Filaggrin gene impairment, and Calcineurin-mediated Th2 cell activation. History taking and clinical manifestations play an essential role in ruling out common differential diagnoses because there is no specific diagnostic tool for AD. The management of AD varies in children and adults depend on the severity of cases. Successful treatment of AD requires multifocal modalities from non-pharmacologic and pharmacologic therapy as well as identification and elimination of flare factors. Managementfor AD including moisturizer, topical corticosteroid, non-steroidal immunomodulators (topical Calcineurin Inhibitors), antibiotics to treat secondary infection, systemic immunosuppressive agents (Cyclosporine, Azathioprine, Methotrexate) and targeted biologic therapeutic agent (Dupilumab). Treatment outcome also affected by the severity of the disease and concomitant atopic conditions. A physician needs to inform the patient that the treatment does not produce a cure to the disease, but it can be controlled.

Keyword: Atopic dermatitis, Eczema, Chronic disease, Immunomodulator therapy

INTRODUCTION

Atopic Dermatitis (AD), also known as eczema, is a chronic, relapsing, and itchy inflammatory skin condition. [1] AD develops in childhood, progressing from acute lesions that affect the face and dorsal aspects of the limbs in infancy, to lesions on the face, neck, and flexures in older children. Around 80% of children with AD will persist until adulthood, most often presenting as lichenified lesions on flexures, head, and neck. [2] Currently, there are 10-20% of children have experiencing AD. [3,4] Other study state that the prevalence of AD is estimated to be 10%-30% in children. [5] This disease regarded as a 'children disease' for a long time. [3] Indonesia is one of the countries that have a high prevalence of skin disease. [6] Keles et al reported from 766 child patients that visit the dermatology and venerology division of Prof. Dr. R. D. Kandou Manado General Hospital, approximately 15.27% of patients have AD. [7]

AD has a significant impact on health-related quality of life as several chronic conditions and other dermatologic conditions. [8] Campos et al stated that AD affects the quality of life of both children and their parents, it can lead to depression and anxiety in children. [9,10] Children with AD were, on average, 65,2% more likely to developmental disorders, compared with children without AD. [11] The main objective of this review is to describe the diagnosis and management of AD to prevent further complications.

ETIOLOGY AND PATHOGENESIS

Research from the past decade has gleaned evidence of genetic, environmental, and immunologic factors that contribute to

the pathogenesis of AD. [5,12] Genetic and mechanistic studies suggest that two major biologic pathways are responsible for AD: epidermal dysfunction and altered innate or adaptive immune responses to microbes, allergens, stress, and irritants. [13] Strong family history of atopy, the onset of disease before 12 months of age, and mutation of filaggrin (FLG) gene are reliable predictors of disease severity. [12]

Exogenous factors such as harsh soaps, detergents, and wool can cause itching and scratching leading to disruption of the skin barrier and initiating a flare. [12,13] The endogenous factor of AD including stress, infections, and food allergies. [5,12]

Table 1. Diagnostic Standard of Hanifin&Rajka [13,15]

Must have three or more basic features described below 1) Pruritus 2) Typical morphology and distribution Flexural lichenification in adults Facial and extensor eruption in infants and children 3) Chronic or chronically relapsing dermatitis 4) Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)
Must have three or more following minor features 1) Xerosis 2) Ichthyosis/palmar hyper linearity, keratosis pilaris 3) Immediate (type I) skin test reaction 4) Elevated serum IgE 5) Early age of onset 6) Tendency toward cutaneous infection (especially *staph. Aureus* and *herpes simplex*), impaired cell-mediated immunity 7) Tendency toward non-specific hand or foot dermatitis 8) Nipple eczema 9) Cheilitis 10) Recurrent conjunctivitis 11) Dennie-Morgan infraorbital fold 12) Keratoconus 13) Anterior subscapular cataracts 14) Orbital darkening 15) Facial pallor, facial erythema 16) Pityriasis alba 17) Anterior neck folds 18) Itch when sweating 19) Intolerance to wool and lipid solvents 20) Perifollicular accentuation 21) Food intolerance 22) Course influenced by environmental and emotional factors 23) White dermographism, delayed blanch

Decreased Skin Barrier Function

Atopic dermatitis is associated with a decreased in skin barrier function caused by the downregulation of cornified envelope genes (FLG), reduce ceramide levels, increased endogenous proteolytic enzyme activity, and enhanced transepidermal water loss (TEWL). [5,13]

Filaggrin Gene Impairment

FLG gene is the key to maintain the protective function of the stratum corneum. FLG gene mutation or dysfunction leads to increasing skin pH, decreasing resistance to *Staphylococcus aureus*, and causing disorders of keratinization that lead to the atopic triad of AD. Diminished intracellular lipids, particularly ceramides, also contribute to increased permeability and water loss in AD. [12]

Calcineurin-mediated Th2 Cell Activation

This activation down-regulates the expression of FLG, resulting in increased TEWL. Th2 cells produce cytokines, which irritate tissue and increase IgE synthesis, maintaining the inflammatory response. Interleukin-4 and interleukin-13 aremajor causes of inflammation and itch in patients with AD. [5,12] Overactivity of the enzyme phosphodiesterase-4(PDE-4) also contributes to inflammation in AD. [12,14]

DIAGNOSIS AND EVALUATION

Specific test is unavailable for AD. The diagnosis is based on specific criteria that take into account the patient's history and clinical manifestations. [4] Several standards and guidelines for the diagnosis of AD have been published. [15] Hanifin and Rajka criteria was used as the standard diagnostic tool in a hospital setting and has 93–96% sensitivity (Table 1). [16] SCORAD (SCORing Atopic Dermatitis) is a widely used clinical tool used to assess the extent and severity of eczema. It measures objective signs as well as subjective symptoms such as itch and sleeplessness. [17]

Clinical manifestation of AD varies with age. In infants (0-2 years), the scalp, face, neck, trunk, and extensor (outer) surface of the extremities are generally affected, while the diaper area is usually spared. Children (2 years to puberty) typically have involvement of the flexural surface of the extremities (i.e., fold/bend at the elbow and back of the knee), neck, wrist, and ankle. In adolescence and adulthood, the flexural surface of the extremities, hands, and feet are usually affected. [4]

DIFFERENTIAL DIAGNOSIS

There are a lot of AD differential diagnosis, such as (1)irritant contact dermatitis, present as acute or chronic eczematous lesions with irritant object applied on the site of exposure and might coexist with AD, (2) allergic contact dermatitis, which is common in children and adults appear as eczematous rash with maximum expression at sites of direct exposure but might spread, have history of locally applied irritants as a risk factor andmight coexist with AD, (3)seborrheic dermatitis, which present commonly ininfants and adults with predilection on the scalp and napkin area in infants and scalp, central face, and anterior chest in adults, (4) scabies, which is common in children with itchy superficial burrows and pustules on palms and soles, between fingers, and on genitalia, might produce secondary eczematous changes, (5)lichen simplex chronicus, which is common in adults as a result from repetitive scratching or rubbing because of intense itch, (6) asteatoticeczema, which common in adults with scaly, fissured patches of dermatitis overlying dry skin, and most often on lower legs, and (7) nummular dermatitis, which is common in children and adults has a coin-shaped scaly patches, mostly on legs and buttocks and no itch. [4,13]

MANAGEMENT

Successful treatment of AD requires a systematic, multipronged approach that incorporates education about the disease state, skin hydration, pharmacologic therapy, and the identification and elimination of flare factors such as irritants, allergens, infectious agents, and emotional stressor. [13]

Education Intervention

Education may be considered as a therapeutic intervention for the management of atopic dermatitis. [13] Educate the patients about the chronic nature of the disease, the importance of treatment adherence, and the appropriate use and application of topical therapies. [4] A study from Australia finds it is important to give adequate education and support as it decreases the severity of eczema in children regardless of the prescribed treatments. [18]

Skin Hydration

There is a dysfunction of skin barrier in AD that manifests as an increase in TEWL and increases penetration of allergens and infectious agents, leading to inflammation and intense pruritus because of filaggrin deficiency and reduced natural skin lipids. [19]

Moisturizers restore the ability of the intercellular lipid bilayers to absorb, retain, and redistribute water. Moisturizers can be divided into several groups (Table 2). [19] It is available in the form of lotions, creams, or ointments. We need extra precaution for some lotions and creams that have

preservatives, solubilizers, and fragrances for the irritating effect. Lotions with high water content may be drying because of an evaporative effect and provide few lipids to the skin. [13] A systematic review study state that moisturizer treatment is beneficial in AD and related disorders. [17]

Class	Mode of action	Biological similarity	Examples
Humectants	Attract and bind water from deeper epidermis to SC	NMF in corneocytes	- Glycerin - Alpha hydroxy acids - Hyaluronic acid - Sorbitol - Urea
Occlusives	Form a hydrophobic film to retard TEWL of SC	Intercellular lipid bilayers - Ceramides - Cholesterol - Free fatty acids	- Carnauba wax - Lanolin - Mineral oils - Olive oil - Petrolatum - Silicone
Emollients	Smoothens skin by filling the crack between desquamating corneocytes	Natural lipids found on skin and sebum	- Collagen - Colloidal oatmeal - Elastin - Glyceryl stearate - Isopropyl Palmitate - Shea butter - Stearic acid

Table 2. Classification of moisturizers [19]

Pharmacologic Therapy

Topical corticosteroids are the first-line pharmacologic treatments for AD. Topical calcineurin inhibitors (TCIs) are immunosuppressant agents that have also been shown to be safe and effective for the treatment of AD, as well as the prophylaxis of AD flares. [4]

Topical Corticosteroid

These agents effectively control atopic flares through their anti-inflammatory, antiproliferative, and immunosuppressive actions. [4] The potency of corticosteroid topical divided into least potent, mild strength, lower midstrength, midstrength, potent or upper midstrength, potent, and superpotent. [13]

Low potency glucocorticoid preparation used on the face, genitalia, and intertriginous area and intermittently for long-term use. Patients should be instructed to apply topical glucocorticoids to their skin lesions and to use emollients or moisturizers on uninvolved skin. [13]

When used appropriately, topical glucocorticoids are extremely safe and effective. The possible local side effect of long-term use includes striae, petechiae, telangiectasia, skin thinning, atrophy, and acne; however, these effects are uncommon with low or moderate potency preparations. [4]

Topical Calcineurin Inhibitors (TCIs)

Topical tacrolimus and pimecrolimus have been developed as non-steroidal immunomodulators. [4,13] Tacrolimus ointment 0.03% has been approved for intermittent treatment of moderate to severe AD in children aged two years and older, with tacrolimus ointment 0.1% approved for use in adults and children 16 years and older; pimecrolimus cream 1% is approved for the treatment of patients aged two years and older with mild to moderate AD. [4,13] Pimecrolimus in infants study from Canada in 2002 concluded that pimecrolimus cream applied twice daily is safe and effective in the treatment of AD in infants aged 3 to 23 months. Early intervention with pimecrolimus to prevent progression to disease flare was proven to be significantly more effective than conventional management with emollients and moderate potent corticosteroids in modifying the long-term course of AD. [20]

The most common local adverse effect of TCIs is transient burning sensation

of the skin and irritation. [4,13] Although both Health Canada and the Food and Drug Administration (FDA) have recommended caution when prescribing TCIs due to rare reports of skin malignancy and lymphoma in patients using these agents, [4] from the cohort of 293,253 patients with AD found no increased risk of lymphoma with the use of TCIs. [13]

Treatment of Skin Infections

The skin of patients with AD is often heavily colonized with *S. aureus*, even at uninvolved sites. Short-term topical and/or oral antibiotic therapy is recommended when an open secondary bacterial infection present. Appropriate systemic antibiotics are indicated for widespread secondary infection, and first- or second-generation cephalosporins or anti-staphylococcal penicillin for 7-10 days are usually effective in managing the infection. [4]

Diluted bleach baths are also recommended to help reduce the number of *S. aureus* skin infection. Systemic antibiotics in patients with heavily colonized skin are needed. Diluted bleach baths involve soaking the patient for 10 minutes in a tub full of lukewarm water that is mixed with one-quarter to one-half cup (60-120mL) of chlorine bleach then patient thoroughly rinsed with fresh water, and apply moisturizer immediately to prevent dehydration and dryness. [4]

Systemic Immunosuppressive Agents

Short-term treatment with systemic immunosuppressive agents, such as cyclosporine, azathioprine, and methotrexate (MTX), has been shown to be effective in patients failing topical treatment and, therefore, these agents are often recommended for severe, refractory AD. [4]

Cyclosporine treatment is associated with reduced skin disease and improved quality of life. Discontinuation of treatment may result in a rapid relapse of skin disease, although some patients may have sustained remission. [4] Based on the results of randomized controlled trials on adult patients, cyclosporine has been approved for the short-term treatment of adults with severe AD with the maximum duration of 1-2 years to avoid the side effects. [21] The side effect of cyclosporine including elevated serum creatinine or significant renal impairment, hypertension, and drug-drug interaction. [4]

Azathioprine is a purine synthesis inhibitor that reduces leukocyte proliferation. [21] Two randomized, double-blind, placebo-controlled studies [22,23] and one single-blinded randomized controlled trial comparing azathioprine with methotrexate [24] showed that azathioprine was superior to placebo, with a significant clinical improvement in disease severity (26% and 37% on clinical outcome scales after three months), and had a clinical efficacy equal to that of methotrexate with an expected average reduction in disease activity of about 40%. [21] A retrospective study from Danish with adult outpatients treated with azathioprine (25–200 mg daily) for severe AD showed that after one year of treatment approximately 52% of patients retained clinical benefit and had no significant adverse effects. [25]

MTX is an antimetabolite, interfering with folic acid metabolism that regulates the immune system and inflammatory processes. A study in 2016 found that MTX treatment in patients with severe AD in which half of the patients benefited from this treatment and after one year of use, discontinuation due to subjective side-effects is uncommon and treatment appears to be long-lasting and effective. [26] Side effects of MTX including hematologic abnormality and hepatic toxicity. [4,13]

Targeted Biologic Therapeutics Agent

Anti-IL-4R a therapy Dupilumab is a fully human monoclonal antibody directed against the alpha subunit of the interleukin-4 (IL-4) receptor. [4,13] the IL-4 and IL-13 receptors share this subunit, thus, it blocks cytokine signaling through both of these receptors. Dupilumab is an FDA-approved

systemic agent for AD treatment, dosed every other week and delivered as a subcutaneous injection. It is indicated for the treatment of adult patients with moderate to severe AD whose disease is not adequately controlled with topical prescription therapy. [13] Dupilumab has been approved in Canada for the treatment of moderate to severe AD. [4] Two phase 3 trials found dupilumab to significantly improve symptoms and quality of life in patients with AD compared to placebo. [4,13]

CONCLUSION

This review highlights the clinical findings and management of AD including its pathogenesis.AD has multifactorial causes and the clinical manifestation vary in children and adults. The management of AD also varies in children and adults and the severity of disease also needs to be measured to make a proper treatment regimen. Treatment outcome also affected by the severity of the disease and concomitant atopic conditions. The physician needs to inform the patient that the treatment does not produce a cure to the disease, but it can be controlled.

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How to cite this article: Sutanto SS, Ni Gusti PRA. Atopic dermatitis: a review on diagnosis and management. International Journal of Research and Review. 2020; 7(6): 113-119.

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