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ATOPIC DERMATITIS

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Abstract: Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease with a wide range of severity, and is usually the first manifestation of atopic disease. It is one of the most common skin disorders in developed countries, affecting approximately 20% of children and 1–3% of adults. Symptoms such as eczematous papules, plaques, and itch, and their associated consequences, such as sleep disturbance, can significantly impact the quality of life of the patient and family.

Key words: atopic dermatities, epidemiology,phenotypes,clinical features

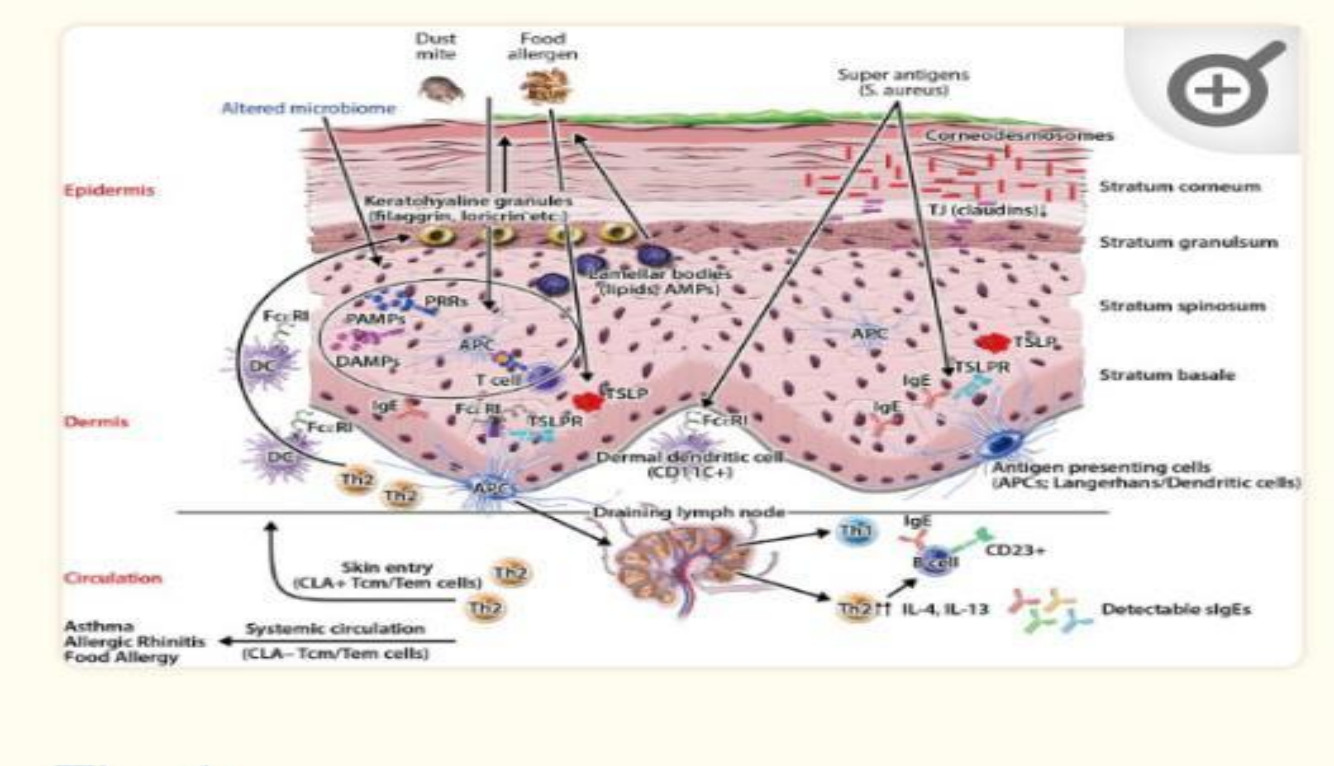
Introduction

Atopic dermatitis (AD), which is a specific form of eczema, is the most common chronic inflammatory skin disease.

This chronic disorder associated with pruritus usually starts in infancy and presents with dry skin, eczematous lesions and lichenification. It is believed that AD is associated with other IgE associated disorders like allergic rhinitis, asthma, and food allergies. AD has significant morbidity and it appears that the prevalence of the disorder has been increasing over the past few decades.

Atopic dermatitis, also known as eczema and atopic eczema, is one of the most common inflammatory disorders, affecting up to 20% of children and 10% of adults in high-income countries.1, 2 Globally, the prevalence of atopic dermatitis is increasing, although estimates in high-income countries are stabilizing. The disorder is characterized by intense itching and recurrent eczematous lesions and has a heterogeneous clinical presentation.[3] Although atopic dermatitis can occur at any age, the usual age of onset is in early childhood, typically at age 3–6 months. Evidence suggests that atopic dermatitis in adults is common, including both persistent and new-onset forms.

The causes of atopic dermatitis are complex and multifactorial. There is a strong genetic component, with evidence for multiple mechanisms of genetic risk. Loss-of-function mutations in the gene encoding



filaggrin (FLG) are the most strongly and consistently reported genetic variants, supporting a key role for the skin barrier, as filaggrin is a major structural protein in the epidermis.[6] Although genetics are clearly important in atopic dermatitis, the increasing global prevalence of the disorder highlights the role of environmental factors. Individuals with atopic dermatitis are at increased risk of having asthma, allergic rhinitis, and food allergy, and could be at increased risk of a wide range of health and psychosocial outcomes.

Fig no;1 Impaired skin barrier enhances allergen penetration and activates the innateimmune system. Multiple factors, including immune dysregulation, defects in terminal epithelial differentiation such as lack of filaggrin (FLG), deficiency of antimicrobial peptides (AMPs), altered composition of stratum corneum intercellular lipids, and altered skin microbiome cause skin barrier defects. Source: Czarnowicki et al. J Allergy Clin Immunol 2017;139:1723–34.

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. About 80% of disease cases typically start in infancy or childhood, with the remainder developing during adulthood. Whereas the point prevalence in children varies from 2.7% to 20.1% across countries, it ranges from 2.1% to 4.9% in adults. The disease displays a high heterogeneity in its natural course and individual trajectories are unpredictable. AD is characterized by sensitive and dry skin, localized or disseminated eczematous lesions usually accompanied by a severe itching sensation. The heterogeneous clinical phenotype varies by age, severity

and ethnic background. AD has a significant impact on the quality of life of the patients and their relatives and represents an important socio-economic burden with an average yearly total (direct and indirect) cost per patient of €15,000 .

Etiology

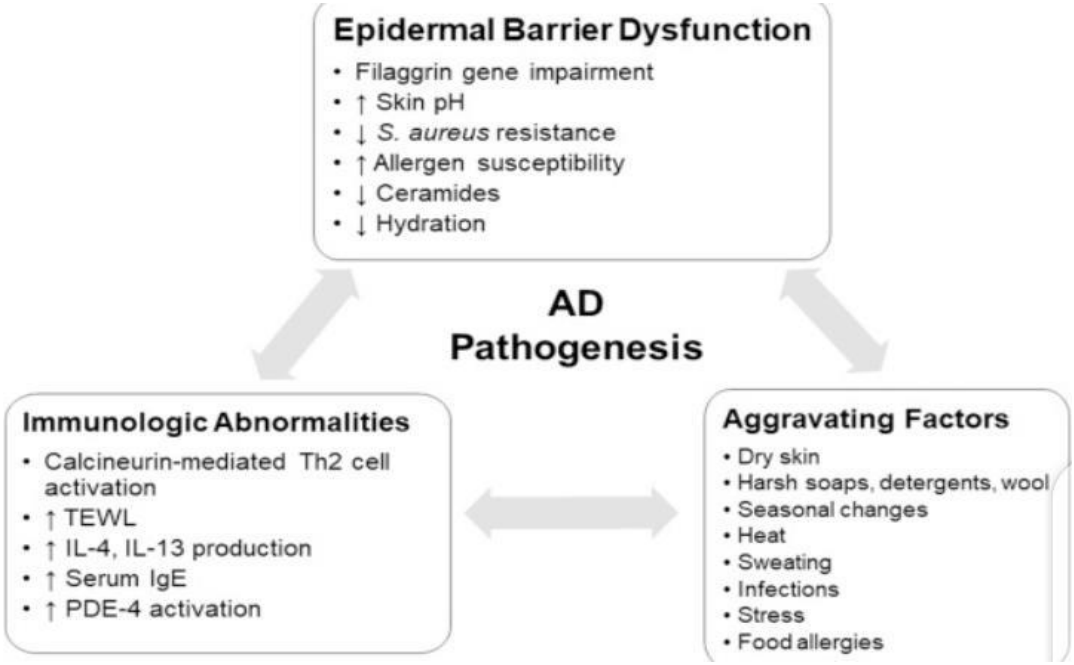
Atopic dermatitis has a complex etiology including genetic and environmental factors which lead to abnormalities in the epidermis and the immune system. Atopic dermatitis is part of the atopic triad (atopic dermatitis, allergic rhinoconjunctivitis, and asthma) which may start simultaneously or in succession in what is known as the "atopic march." Patients with the atopic triad have a defective barrier of the skin, upper respiratory, and lower respiratory tract which leads to their symptomatology. If one parent is atopic, there is more than a 50% chance that their offspring will develop atopic symptoms. If both parents are affected, up to 80% of offspring will be affected. Genetic alterations include loss of function mutations of filaggrin (Filament **Ag**gregating Prote**in**), an epidermal protein that is broken down into natural moisturization factor. Filaggrin mutations are present in up to 30% of atopic dermatitis patients and may also predispose patients to ichthyosis vulgaris, allergic rhinitis, and keratosis pilaris. Food hypersensitivity may also cause or exacerbate atopic dermatitis in 10% to 30% of patients. Ninety percent of such reactions or flares are caused by eggs, milk, peanuts, soy, and wheat.

Epidemiology

Atopic dermatitis affects about one-fifth of all individuals during their lifetime, but the prevalence of the disease varies greatly throughout the world. In several so-called industrialized countries, the prevalence increased substantially between 1950 and 2000 so much that many refer to as the “allergic epidemic.” However, current indications point to eczema symptoms having levelled off or even having decreased in some countries with a formerly very high prevalence, such as the United Kingdom and New Zealand. This indicates that the allergic disease epidemic is not increasing continually worldwide. Nevertheless, atopic dermatitis remains a serious health concern, and in many countries, particularly in the developing world, the disease is still very much on the rise.

Pathophysiology

The pathogenesis of AD is not completely understood, however, the disorder appears to result from the



complex interaction between defects in skin barrier function, immune dysregulation, and environmental and infectious agents . Skin barrier abnormalities appear to be associated

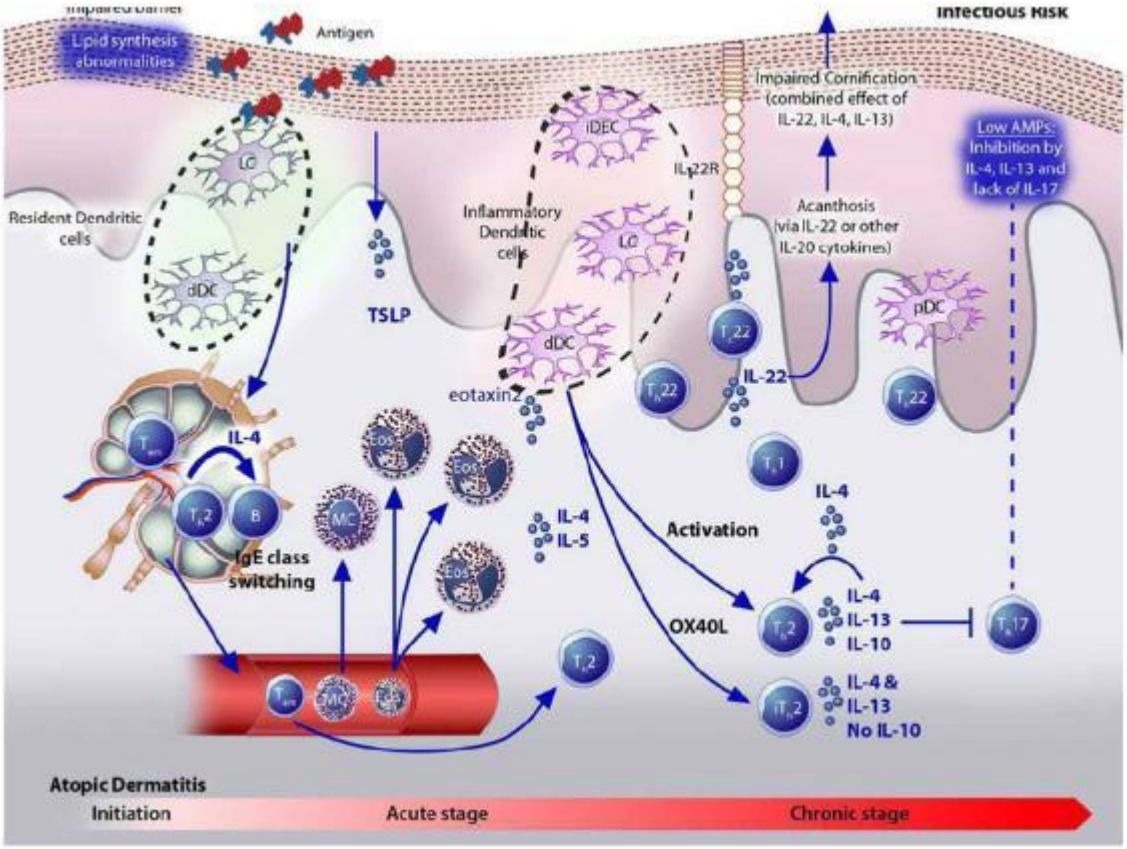


Figure no 2;Pathophysiology of a topic dermatitis

with mutations within or impaired expression of the filaggrin gene, which encodes a structural protein essential for skin barrier formation. The skin of individuals with AD has also been shown to be deficient in ceramides (lipid molecules) as well as antimicrobial peptides such as cathelicidins, which represent the first-line of defense against many infectious agents. These skin barrier abnormalities lead to transepidermal water loss (passage of water from inside the body through the epidermal layer of the skin to the surrounding atmosphere) and increased penetration of allergens and microbes into the skin. The infectious agent most often involved in AD is *Staphylococcus aureus* (*S. aureus*), which colonizes in approximately 90% of AD patients. Defective innate immune responses also appear to contribute to increased bacterial and viral infections in patients with AD. This interplay of factors leads to T cell responses in the skin (initially a predominantly T helper-2 [Th2] response and later a predominantly Th1 response) with resultant release of chemokines and proinflammatory cytokines (e.g., interleukin [IL]-4, IL-5 and tumour necrosis factor) that promote immunoglobulin E (IgE) production and systemic inflammatory responses, leading to pruritic inflammation of the skin.

Two main hypotheses have been proposed to explain the inflammatory lesions in atopic dermatitis. The first hypothesis concerns an imbalance of the adaptive immune system; the second hypothesis concerns a defective skin barrier. Although these two hypotheses are not thought to be mutually exclusive, they may complement each other.

1.Immunological Hypothesis

The theory of immunological imbalance argues that atopic dermatitis results from an imbalance of T cells, particularly T helper cell types 1, 2, 17, and 22 and also regulatory T cells . In the allergic (atopic dermatitis) state—particularly in acute eczema—the Th2 differentiation of naive CD4+ T cells predominates. This causes an increased production of interleukins, primarily IL-4, IL-5, and IL-13, which then leads to an increased level of IgE, and the Th1 differentiation is correspondingly inhibited.

2.The Skin Barrier Hypothesis

The theory of skin barrier defects is more recent and has its origin in the observation that individuals with mutations in the *filaggrin* gene are at increased risk of developing atopic dermatitis . The *filaggrin* gene encodes structural proteins in the stratum corneum and stratum granulosum that help bind the keratinocytes together. This maintains the intact skin barrier and the hydrated stratum corneum. With gene defects, less filaggrin is produced, leading to skin barrier dysfunction and transepidermal water loss, which causes eczema. There is evidence to suggest that the impaired skin barrier, which results in dry skin, leads to increased penetration of allergens into the skin, resulting in allergic sensitization, asthma, and hay fever . Preventing dry skin and active eczema early in life via application of emollients may constitute a target of primary prevention of progression of eczema into allergic airways disease.

3.normal skin barrier

The skin barrier plays a critical role in preventing allergen and microbial penetration into the human body. The epidermis consists of a 15- to 30-nm-thick layer of proteins and lipids, and provides a physical and functional barrier to the human body. The physical skin barrier is mainly localized to the uppermost area of the epidermis which is the cornified layer (stratum corneum). The epidermis is continuously regenerated by terminally differentiating keratinocytes, which is known as cornification or keratinization. Cornification begins with the migration of keratinocytes from the basal to upper layers, and ends with the formation of the cornified layer. During epidermal differentiation, lipids are produced by keratinocytes and extruded into the extracellular space to form extracellular lipid-enriched layers. Omega-

hydroxy-ceramides are covalently bound to cornified envelope proteins and form the backbone for the subsequent addition of free ceramides, free fatty acids, and cholesterol in the cornified layer. The epidermis undergoes complete turnover every 28 days.

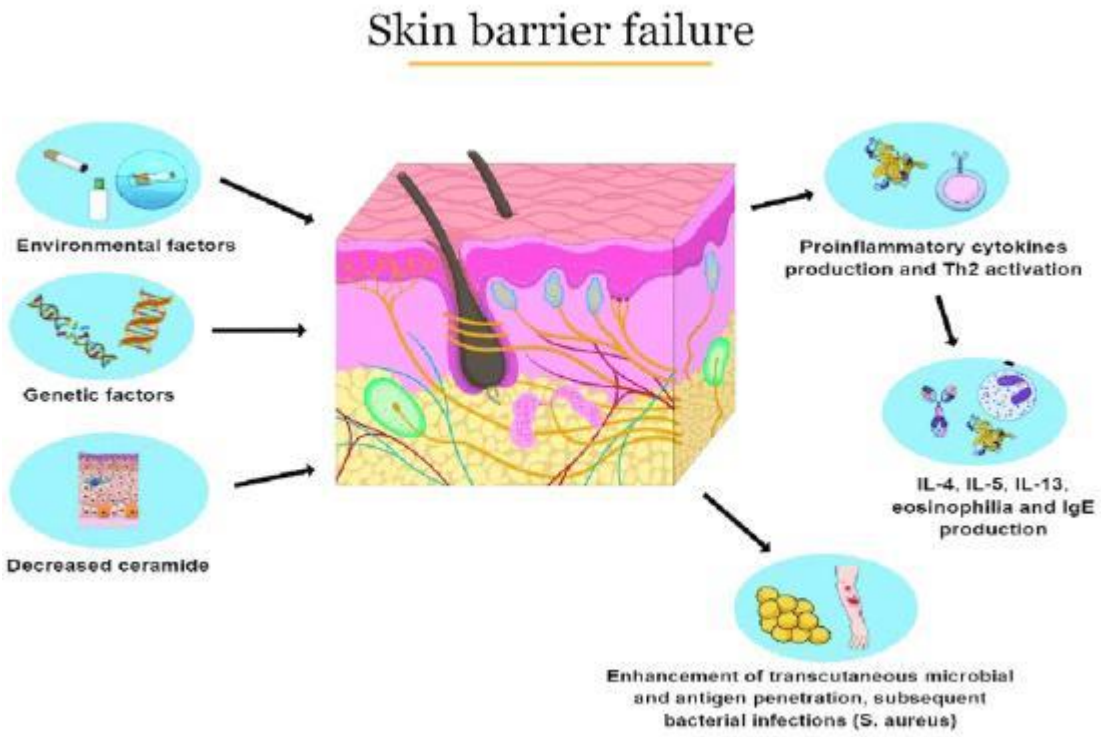


Figure no 3;skin barrier hypothesis

4. Dysregulation of the skin barrier

Epidermal barrier proteins, including FLG, TGs, keratins, loricrin and intercellular proteins, are cross-linked to form an impermeable skin barrier. Skin barrier defects facilitate allergen sensitization and lead to systemic allergic responses, such as increased IgE levels and airway hyperreactivity. Transepidermal water loss (TEWL) is a noninvasive measurement used to evaluate skin barrier function. Patients with AD have increased TEWL, which reflects skin barrier dysfunction in AD, and can precede clinical AD.

Histology

Histology of both forms of dermatitis is highly similar to that of allergic contact dermatitis and has no fundamental impact on the diagnosis of AD. Clinically "normal" appearing skin of AD patients contains a sparse perivascular T-cell infiltrate suggesting minimal inflammation. "Acute" popular skin lesions are characterized by marked intercellular edema (spongiosis) of the epidermis. Langerhans cells (LC), in lesional and, to a lesser extent, in nonlesional skin of AD exhibit surface-bound IgE molecules in the IgE-associated form but not in the non-IgE-associated form. In the dermis of the acute lesion, there is a marked perivascular T-cell infiltrate with monocyte-macrophages. The lymphocytic infiltrate consists predominantly of activated memory T cells bearing CD3, CD4, HLA-DR, CD25 and CD45RO. Eosinophils are seen in the acute lesions but basophils and neutrophils are rarely present. Mast cells are present in various stages of degranulation.

"Chronic" lichenified lesions are characterized by a hyperplastic epidermis with elongation of the rete ridges, prominent hyperkeratosis, and minimal spongiosis. There is an increased number of IgE-bearing DC in the epidermis, and macrophages dominate the dermal mononuclear cell infiltrate. The number of mast cells is increased but the cells are generally fully granulated. Although they are hardly seen histologically, increased numbers of eosinophils are suspected in the dermis of chronic AD skin lesions since their products such as eosinophil major basic protein, eosinophil cationic protein and eosinophil-derived neurotoxin can be detected by immunostaining. Thus eosinophils may likely contribute to allergic skin inflammation by the secretion of cytokines and mediators that augment allergic inflammation and induce tissue injury in AD through the production of reactive oxygen intermediates and release of toxic granule proteins.

Diagnosis

Diagnosis of AD relies primarily on the patient's and family's history as well as on clinical findings. The clinical diagnosis of AD is based on the clinical phenotype according to the morphology and distribution of the lesions at the different stages (see above). In 1980, Hanifin and Rajka proposed major and minor diagnostic criteria based on clinical symptoms of AD. A revision of the diagnostic criteria was accomplished by Williams. Severity of AD can be evaluated by different scoring systems such as the Score in Atopic Dermatitis (Score in Atopic Dermatitis: SCORAD) or the Eczema Area and Severity Index

(EASI). These scoring systems can be of help in the daily praxis but are mandatory in clinical trials. The overall atopic status is best appreciated by using the validated Diepgen score.

Skin tests and laboratory investigations (specific IgE) are helpful in the search of provocation factors such as food or environmental allergens. Provocation tests are additionally performed to determine the clinical significance of positive laboratory tests since skin tests and *in vitro* testing should complement one another yet do not always have to be concordant. The atopy patch test (APT) is about to be standardized for the search of AD-relevant allergen. While the sensitivity of APT is rather average, its specificity is high for the individual context of a given patient. Most importantly, laboratory results have always to be interpreted in the context of the patient's history and skin tests.

There are no specific diagnostic tests for AD. Diagnosis of the disorder is based on specific criteria that take into account the patient’s history and clinical manifestations. Although various diagnostic criteria for AD have been proposed and validated, the application of many of these criteria is time consuming and often necessitates invasive testing. Table 1 provides simplified criteria proposed by Williams et al. that are easy to use, do not require invasive testing, and have been shown to have a high sensitivity and specificity for the diagnosis of AD . Using these criteria,

Major criteria
Patient must have
• An itchy skin condition (or parental/caregiver report of scratching or rubbing in a child)
Minor criteria
Plus three or more of the following minor criteria
Older children/adults
• History of itchiness in skin creases (e.g., folds of elbows, behind the knees, front of ankles, around the neck)
• Personal history of asthma or allergic rhinitis
• Personal history of general dry skin in the last year
• Visible flexural dermatitis (i.e., in the bends or folds of the skin at the elbow, knees, wrists, etc.)
• Onset under age 2 years
Children < 4 years[a]
• History of itching of the cheeks
• History of atopic disease in a first-degree relative
• Eczema of cheeks, forehead and outer limbs

Table:1;diagnosis of atopic dermatitis

Treatment and management

The four major components of treatment include trigger avoidance, daily skin care, anti-inflammatory therapy, and other complementary modalities.

Daily skin care includes the application of emollients twice daily, with the application within three minutes of exiting lukewarm shower or bath to prevent skin drying. Ointments are the most occlusive but may be more greasy. Topical steroids, which should be applied before emollients to "lock-in" their effect, are first-line agents for acute flares. The potency should be strong enough to control a flare quickly, and consideration should be given for tapering every other day and for maintenance therapy twice weekly (e.g., weekends) in the usual areas of involvement. Reversible side effects of steroid use include skin atrophy and telangiectasia.

Sensitive areas (including the intertriginous areas of the axilla and groin, in addition to the face) may require topical nonsteroidal agents including calcineurin inhibitors such as tacrolimus and pimecrolimus. Newer non-steroidal agents include crisaborole, which exerts its effect by blocking PDE-4. When atopic dermatitis is not controlled with topical agents, systemic agents include phototherapy (ultraviolet (UV) A, UVB, and narrow-band UVB), cyclosporine, azathioprine, mycophenolate mofetil, and methotrexate.

A newly FDA-approved biologic therapy is dupilumab, which is a monoclonal antibody that blocks the IL-4 receptor and thus the effect of IL-4 and IL-13. Other complementary therapies include bleach baths (0.5 cup bleach in full 40 gallon tub) one to two times weekly to decrease *S. aureus* colonization, low allergen maternal diets during breastfeeding, and probiotic and prebiotic use in pregnant mothers and at-risk infants which has shown 50% decreased frequency of atopic dermatitis at ages 1 to 4 years old compared to placebo.s

Recently Crisaborole topic ointment was approved for mild to moderate AD. The drug is a phosphodiesterase inhibitor and shown to improve skin symptoms.

Some patients may benefit from probiotics; it is believed that the bacterial products may enhance the immune system and prevent the development of allergic IgE antibody response. Further, probiotics are recommended during pregnancy and in breast feeding women.

Numerous studies show that bleach baths may help relieve the symptoms of AD by lowering the risk of superinfection with bacteria.

Conclusion

Atopic dermatitis is one of the most common chronic diseases with a high global burden in health-care costs and morbidity. Although many areas of uncertainty persist (panel 2), discoveries from genetics, molecular biology, epidemiology, and clinical medicine have spurred new disease concepts, including the notion of endotypes, and a broader understanding of health and psychosocial outcomes in atopic dermatitis. In most patients, atopic dermatitis constitutes a lifelong disposition with variable

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