# ETIOPATHOGENIC AND THERAPEUTIC CONSIDERATIONS IN ATOPIC DERMATITIS

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***Abstract:*** *Atopic dermatitis is a pathology commonly found in dermatological practice, with an ever increasing incidence in our country. For mild and moderate forms of atopic dermatitis, numerous topical and systemic products are available to control and cure the acute episode, but also to maintain a prolonged remission. For severe forms of atopic dermatitis, refractory to standard therapies, a number of new efficient treatments are currently available proven by clinical trials and practical application only for selected cases. Through this paper we wanted to synthesize the latest data from the literature on atopic dermatitis etiopathogenesis, the internal and external trigger factors involved and the therapeutic methods that can be used for a correct and individualized management of atopic dermatitis.*

## INTRODUCTION

Atopic dermatitis (AD) is an inflammatory dermatosis commonly found in dermatological practice, with chronic, recurrent, pruritic evolution that occurs most frequently in the first childhood and can continue/ relapse in preschool period or adulthood. From the etiopathogenic point of view, a multitude of favoring factors and complex pathogenic pathways are involved, and from a clinical point of view it is a disorder resulting from the alteration of the skin barrier with typical age-dependent clinical manifestations with varying degrees of severity.

Depending on the onset moment, the following forms are known:

- Early onset after 2 months of age - AD of infant and young child (up to 2 years of age) with erythematous-vesicular, exudative lesions, sometimes with ulcerations after scratching covered with hematic crusts or sometimes at risk of impetiginization, with preferential location at the level of convex areas of the face,
- early onset forms - AD of the child over 2 years of age (most commonly around the age of 7 years) with erythemato-squamous, licheniform, extremely pruritic plaques, located in flexural areas
- forms with late onset - AD of the adult, localized symmetrically in the cephalic extremity (often occipital), shoulder girdle, back of the hands.

The etiopathogenicity of this condition is still incompletely elucidated, but it is now accepted that the starting point is the skin barrier dysfunction.(1) Some researchers believe that there is a disorder of the innate and acquired immune response that interacts with the suboptimal cutaneous barrier function.(2)

On a specific genetic background (IL-4 gene, CD14, specific HLA, FcεRI-β alterations) and under conditions of deficiency of filaggrin essential in the skin barrier function, a number of environmental factors (allergens, excessive hygiene, with degreasing products etc.) and triggers (infections, stress, wet and polluted climate, hormonal factors etc.) that trigger the acute episode or relapse episodes in AD.

Recent studies (3) argue that in AD pathogenesis an important part is played by the skin barrier deterioration, exacerbated innate immune response (Th2) and microbial disbiosis. In the acute, inflammatory phases of the AD there is an imbalance of the cutaneous microbiome, with the excessive multiplication of Staphylococcus aureus and Staphylococcus epidermidis strains and the absence of saprophytes, polymicrobial flora normally present on healthy skin without inflammatory lesions (Corynebacterium, Dermaccocus, Streptococcus).

In terms of topical therapy in AD, the main products used to control skin inflammation and pruritus are the dermatocorticoids. There is a wide range of emollients with quick and lasting effects that can control xerosis and secondary pruritus to restore the skin barrier. For the control of moderate to severe forms of AD, systemic corticotherapy, methotrexate, mycophenolate mofetil, ciclosporin and azathioprine can be used. They are effective but their use is sometimes limited by their side effects (skin or systemic immunosuppression, pluriorganic toxicity etc.), especially on their long-term administration. Regarding the systemic therapeutic arsenal that can be used in AD, Dupilumab represents the culmination of several decades of scientific research into the biology field of allergic diseases, as well as the moderate to severe AD.

Combined probiotics and prebiotics are promising therapies in AD but further studies are needed to clarify the strains, dosage and target populations.

## AIM

The aim of the paper is to synthesize data from the literature on the etiopathogenesis of AD, the triggering factors and the therapeutic methods that can be used for a good management of this disease.

## MATERIALS AND METHODS

We have reviewed 5 clinical trials, 8 reviews and the European Guidelines for AD, published in the specialty literature over the last 10 years. We used the search engines Medscape, Pubmed, Derm101 and Science Direct, and as keywords "AD etiopathogenesis", "New AD therapies", "Treatment guide", "Biological therapies" and "AD". We highlighted the novelties regarding the etiology and risk factors

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implications in the onset of AD and synthesized the main therapeutic lines recommended by the new international therapeutic guidelines.

## RESULTS AND DISCUSSIONS

In terms of AD etiopathogenesis and treatment, a series of extensive studies of cell biology and immunopathology have highlighted the complexity of anomalies involved in the pathogenesis of the disease. AD is the result of complex interactions between skin barrier function defects, immune anomalies and the action of environmental and infectious agents. In the prenatal period, the fetus is protected from external factors by the immune system of the mother, the peptides and antimicrobial proteins in the amniotic fluid. Additionally, antimicrobial proteins (defensin and cathelicidin) are synthesized at the fetal epidermis level.

The first colonization of the newborn with bacteria from the mother's flora occurs in the natal period and in the post-natal period, by breastfeeding. At the intestinal level, an intestinal microbiota is formed with antimicrobial role and stimulating the development of the immune system. Any disruption of the microbiota favours the invasion of pathogens at this level.(4)

From an immunological point of view, maternal immunoglobulins in the last trimester of pregnancy are gradually replaced by their own immunoglobulins, initially by immunoglobulin M (IgM), then immunoglobulin G (IgG), and finally de novo immunoglobulin A (IgA) is produced. Because of the immunoglobulin production deficiency characteristic of the neonatal period, the sensitivity and reception of young children is higher to develop infectious diseases.

Little et al suggest that exclusive breastfeeding is not an identifiable risk or a protective factor in AD development in children.(5) Contrary to these findings, concomitant studies have shown that breastfeeding during the first four months of life may result in a 33% reduction in the incidence and severity of AD in high-risk individuals. Taking into account current studies, exclusive breastfeeding for 4 to 6 months, may greatly reduce the risk of AD.

The ability to develop atopy in life is determined by many factors, both internal and external.

*Internal factors* represent genetic susceptibility, inherited by sequential DNA variation and the formation of new genes. To these changes the variations of the intrauterine environment are added under the influence of factors such as: the mother's allergic and astmatic status, the influence of nutrition, the socio-economic status, and the stress the mother is exposed to.

*External factors* (air, exposure to animals, repeated viral infections, presence of mold in the home, type of diet, daily care, stress) also favour the epigenetic modification of DNA by gene methylation and histone modification. There is a change in the gene expression of blood leukocytes, with the formation of intermediate phenotypes, acting on the immune status of the child and on the immune response. Thy / Th2 deviation, specific allergen sensitization from childhood and respiratory airway inflammation are produced. The basis of atopic status with skin sensitization and the presence of high total IgE are set and, hence of the clinical atopic phenotypes: eczema, asthma, asthmatic bronchitis, allergic rhinitis, food allergies, anaphylaxis.(4)

Regarding the *genetic factor* expressed in AD, it is believed that the mutation in the filaggrin gene, a cluster of about 60 genes located on chromosome 1q21, causes damage to the skin barrier, which in combination with the action of environmental factors causes AD. The mutants carry a distinct profile of the disorder, which is persistent, with a higher incidence of herpes virus infections and at increased risk of developing asthma.

In recent years, studies aimed at investigating the possible link between skin microbiome and the occurrence of atopic dermatitis. It has been hypothesized that changing microbial skin diversity can cause atopy rashes. Kong et al. have noticed that any imbalance in the cutaneous microbiome can lead to the appearance of skin bacterial superinfections.(6) It has been found that the diversity of microbial flora decreases, being rapidly followed by the increase in the proportion of staphylococci, at which time the rash occurs. As the eruption decreases, the proportion of staphylococci begins to decrease, along with increasing microbial diversity and returning the microbiome to its normal, physiological composition. It can be concluded that the skin microbial imbalance in the skin contributes to maintaining the vicious circle of atopy.(7)

Microbiome mapping was attempted in atopic dermatitis, starting from the following working hypotheses:

- is the microbiome of atopic lesions different from perilesional skin in the same patient?
- does the microbiome of the atopic skin change after applying an emollient?

Seite et al. confirmed the microbiome diversity hypothesis, independent of its richness, as an indicator of a healthy skin. In atopic patients, microbial diversity in the skin was low, being directly proportional to the severity of atopic dermatitis. In the treatment of patients with atopic dermatitis by using an emollient, the influence on the cutaneous microbe, by significant reduction of staphylococci (epidermidis, aureus, haemolyticus) was observed.(7)

The results of the study of Kong et al. underline the fact that a rational therapeutic approach to atopic dermatitis consists in modulation of the cutaneous microbiome, with the increasing diversity of the bacterial species that make it, along with the reduction in the proportion of pathogenic staphylococci. This allows stimulation of the immune system of the skin in parallel with the regulation of cutaneous homeostasis, which interrupts the vicious pathophysiology of AD.(6)

There are studies that say that in children predisposed to AD there is a low basal production of interferon (IFN). IFN is produced by Th1 lymphocytes, which has a role in regulating IgE production. This decrease is due to increased secretion of prostaglandin E2 and IL-10 by monocytes. The decrease in IFN production is inversely correlated with serum IgE levels, resulting in an increase in IgE synthesis. In AD patients, total serum IgE levels correlated with CD86 expression on B cells, suggesting a role in IgE synthesis. In AD, persistence of a Th2-type response suggests an intrinsic defect in T-cell function and is characterized by an increased secretion of IL-4, IL-5 and IL-13.

*Atmospheric pollution* is another factor involved in AD etiopathogenesis. It has been found that a number of atmospheric pollutants, whether in the form of particles or gases, either inside or out, are related to the development or exacerbation of AD. These pollutant chemicals in the atmosphere include nitrogen oxide compounds, fine particulate matter, carbon monoxide, toluene, volatile organic compounds, benzene and its metabolites, formaldehyde, sulfur dioxide and tobacco smoke.

Also, food additives are included among trigger factors involved in AD pathogenesis. A multitude of chemicals added to foods to improve the organoleptic properties of these may be associated with non-allergic food hypersensitivity. These additives include preservatives, antioxidants, artificial dyes, stabilizers, flavorings, emulsifiers and artificial

sweeteners.(8)

**AD management**

AD management is not standardized, choosing the best treatment depending on the severity of the manifestations, the associated risk factors, compliance and adherence to the patient's treatment, as well as the experience of the treating physician.

Treatment should be individualized according to clinical form, location, severity of skin lesions, and psychological impact on patients / parents life.

The current objectives of AD treatment are:

- fighting skin inflammation,
- remission of pruritus,
- restoring the skin barrier with xerosis improvement.(9)

►**Topic treatment:** is the basic treatment for all evolutive stages of AD.

*Emollients* are used in AD therapy to improve skin barrier function and to restore the epidermal lipid layer (applied both in the remission period and in the absence of symptoms, at least 1-2 times a day). It has been shown that emollients modify the microbial diversity associated with atopic lesions, reducing staphylococci and restoring microflora diversity (growth of predominant Corynebacterium sp or Sterotrophomonas sp).(10)

*Topical corticosteroids (TCS)* remain the gold standard in anti-inflammatory treatment of AD since the introduction of hydrocortisone in the 1950s. They represent a complex therapeutic action with spectacular efficiency but also redoubtable in terms of side effects. It is important that the choice of TCS is made according to the age of the patient (skin penetration in children is higher, whereas in the elderly the risk of atrophy and purpura is higher and the removal of the active substance from the skin is more difficult). For these age groups, low or medium potency TCSs, and preferably non-chlorinated, are preferred.

In general, topical dermatocorticoid treatment should be sequential: for short periods of time if high and medium potency products are used or may be prolonged with low doses for medium and low potency products. Among the side effects of topical corticosteroid treatment, we mention the following: cutaneous atrophy, telangiectasia, hypertrichosis, acneiform eruptions, perioral dermatitis. Systemic side effects of TCS occur in the case of using superpotentiated topical corticosteroids, especially in infants and children, and include reversible inhibition o hypothalamic–pituitary–adrenal axis, Cushing's syndrome, cataract / glaucoma.(11)

*Topical calcineurin inhibitors:* are part of the macrolactam family, being ascomycin derivatives, and are represented by tacrolimus and pimecrolimus.(11,12) As a mechanism of action, calcineurin inhibitors inhibit T lymphocyte activation by interfering with calcineurin, a calcium-dependent phosphatase, necessary to activate lymphocytes.

Tacrolimus ointment is recommended in a concentration of 0.03% in children aged between 2 and 15 years, and in a concentration of 0.1% over the age of 15 years. The use of tacrolimus in AD has been shown to be effective, significantly reducing the clinical manifestations, with the possibility of long-term use without skin atrophy, a common reaction when using TCS.

Pimecrolimus 1% cream, used after the age of 2, is almost structurally identical to tacrolimus (two additional chemical groups that alter its affinity for lipids and skin penetration capacity), with a more pronounced lipophilicity that results in a higher affinity to the skin.

As possible side effects, patients most commonly suffer burning or stinging at the application site. In case of long-term use of calcineurin inhibitors, the potential carcinogenic side effects remain questionable, being subject to long-term studies.(11)

Recently, the topical treatment with Crisaborole (2% ointment), the first of a new class of phosphodiesterase 4 (PDE4) topical inhibitors, was evaluated and approved by the FDA. In a vehicle-controlled phase 3 clinical trial (13) in AD patients aged over 2 years, the investigator's static global assessment (ISGA) increased to 51.7% and 40.6% and 48.6% compared with 29.7% in the treatment group versus the vehicle group.

Myriphytase (the active ingredients consist of a mixture of lipidized fatty acids and flavonoids) is a new cream approved by the FDA.(14) The cream was applied twice / day for 5 weeks to 20 patients with mild to severe AD, between the ages of 18 and 75 years. Statistically significant improvements in visual analogue scale (VAS) scores in weeks 2-4 and atopic dermatitis SCORing (SCORAD) + dermatology life quality index (DLQI) were observed on day 30.

► **Phototherapy** is available to patients with AD without response to topical and systemic corticosteroids or to patients who cannot avoid all etiologic agents in their daily activity. Patrizi et al. have underlined the effectiveness of PUVA and UVB in the treatment of chronic AD, ultraviolet radiation having immunosuppressive and anti-inflammatory properties.(15)

UVB phototherapy (with a wavelength of 290-320nm) inhibits the activation of T cell effectors. This effect is also due to the direct action on dendritic cells (antigen presenting cells) and indirectly by the production of IL-10 and prostaglandin E2 that diminish antigen expression, thereby inhibiting T lymphocyte response to the antigenic stimulus. The calculated dose of recommended UVB radiation is dependent primarily on the cutaneous phototype (constitutional melanogenic pigmentation and skin response to exposure to UV radiation).

UVA radiation (320 - 400nm) can penetrate to the deep dermis, being able to destroy DNA, lipids, structural and nonstructural proteins and cellular organelles such as mitochondria. For therapeutic purposes, UVA phototherapy has anti-inflammatory effects, being used successfully in inflammatory skin diseases, either alone or in combination with photoactive substances (psoralen, meladinin, oxoralen) + UVA = PUVA. The photosensitizing agent is administered two hours before exposure to UVA radiation. Exposure is progressive from a few tens of seconds to tens of minutes, 4x / week, with remissions after 10-25 sessions. It can be continued with maintenance treatment when the last effective dose of treatment is maintained, progressively reducing the sessions. The side effects commonly seen during phototherapy are erythema, edema, pruritus, xerosis, conjunctivitis, lipotomy. Therefore, it is necessary to supervise the patient during the phototherapy session and to adjust the dose applied depending on the reactivity of the skin to the UVB or UVA radiation.

►**Systemic treatment**

It is recommended in moderate to severe AD cases, refractory to topical treatment, mainly after 6 weeks of unresponsive treatment. The main classes of substances indicated in systemic AD treatment are systemic corticosteroids, methotrexate, mycophenolate mofetil, ciclosporin and azathioprine.

Systemic corticosteroids are only given in acute flares at doses of 0.75-1 mg / kg / day in short-term therapy (7-10 days). Methotrexate can be given in AD, studies being published regarding its administration, both in adults and children, at the dose of 7.5-25mg / week in combination with folic acid. Mycophenolate mofetil is administered in the initial dose of 2g /

day and then 1g / day, as maintenance therapy. Unfortunately, in Romania, mycophenolate mofetil is not available. Ciclosporin is an immunosuppressant that can be given initially at doses of 3-5mg / kg / day, then lowering the dose to the lowest possible controlling the inflammatory response. They are effective but limited by side effects, including suppression of immune response, oncogenic risk and pluriorganic toxicity.

Antihistamine therapies in AD have a great utility in terms of both pruritus and pathogenic control through their action on mastocytes.

The introduction of biological therapies in AD management has provided a promising approach, especially in the severe, refractory forms to conventional treatments.

Dupilumab is a human monoclonal antibody that inhibits the over-active signaling of IL4 and IL13. It is the first and the only biological product approved by the FDA for the treatment of adults with moderate to severe forms of AD not controlled with topical therapies. It is available in the form of a pre-filled syringe, which can be self-administered subcutaneously twice / month, after an initial attack dose. It was approved on the basis of data from the global clinical programme LIBERTY AD, which included 3 pivotal randomized phase 3 studies: SOLO1, SOLO2 (monotherapy) and CHRONOS (together with TCS). It is currently being evaluated within a programme that includes studies on children with severe AD (6 months - 11 years) and adolescents with moderate to severe AD (12-17 years).(16) Side effects seen in clinical trials include: infections (conjunctivitis, herpes oral), haematological disorders (eosinophilia), immune system disorders (serum sickness), nervous system disorders (headache), eye disorders (eye pruritus, blepharitis), injectitis.(17)

Fezakinumab is a human monoclonal antibody targeting IL-22. The randomized double-blind study published by Guttman-Yassky et al. in 2018, concluded that the treatment with Fezakinumab has encouraging results in the treatment of severe AD forms (SCORAD> = 50). There was a reduction in the SCORAD score: at 12 weeks - 12.6 versus 9.6 in the placebo group; at 20 weeks of 27.4 versus 11.5. There was also a significant decrease in the affected skin area by 12.4% in the treated group versus 6.2% in the placebo group.(18) The most common adverse effects are upper respiratory tract infections.

Treatment with Upadacitinib, a JAK1 enzyme inhibitor, approved by the FDA in January 2018, was also evaluated. In a phase 2b study, an improvement in EASI score was noticed compared with placebo at 16 weeks at all tested doses (30, 15, 75 mg / day).(19)

Omalizumab is an anti-IgE antibody that limits the degranulation of mastocytes and inhibits the release of proinflammatory mediators. It is currently used in the treatment of idiopathic chronic urticaria (12 years of age) and in severely persistent allergic asthma (from age 6). In the specialty literature, cases of severe AD (associated with allergic rhinitis and / or asthma, positive for aeroallergens without response to routine treatments) treated off-label with Omalizumab have been reported, treatment being generally well tolerated, with decreasing serum IgE.

New, randomized, controlled clinical trials are required to use Omalizumab in the treatment of severe AD.(20)

Other therapies that can be used in the severe forms of AD under study are: rituximab, an anti-CD20 molecule and intravenous immunoglobulins, whose efficacy in AD is controversial.

## CONCLUSIONS

Atopic dermatitis is an inflammatory disorder whose management is complex and aims at combating inflammation, pruritus and maintaining a remission state, by preventing the progression of the disease, and last but not least, to increase the quality of life of these patients.

AD treatment should be individualized, with varied therapeutic lines being available nowadays, both local and systemic. For a good AD control, it is necessary to use complementary methods (with a special focus on emollients) and combined therapies. Great advances, especially through the development of biological therapies for severe, refractory forms of AD, open up new horizons in AD therapeutics.

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