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Flare management in atopic dermatitis: from definition to treatment

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***Abstract*:** Atopic dermatitis (AD) is a skin immune-mediated inflammatory disease with a chronic-recurrent course. Acute exacerbations or flares are an integral part of the AD course and are generally defined as disease worsening, requiring escalation/intensification of treatment. Management of flares is crucial since their prevention is a key aim of long-term disease control. Nevertheless, difficulties related to this aspect are several, starting from the definition of flare itself, which is not always satisfactory or unambiguous, and needs clarification. Indeed, this hurdle may reduce clarity on treatment choice and generate difficulties when comparing data between studies. Deepening our knowledge on flares could be highly relevant to both clinicians and patients to provide adequate control of the disease through patient education and appropriate treatment. This review aims to summarize current knowledge on the management of AD flares from definition to treatment, highlighting aspects that are still unclear, and identifying any necessary unmet needs to better manage AD.

Keywords: atopic dermatitis, definition, disease control, flare, prevention, treatment, triggers

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Introduction

Atopic dermatitis (AD) is an immune-mediated inflammatory skin disorder presenting with pruritic recurrent eczematous lesions, but a diverse range of morphologic manifestations may occur.[1–3] Disease onset manifests mainly during childhood, with up to 20% of children affected. From 2% to 8% of adults are affected by AD, and AD starts in adulthood in approximately 25% of these patients.[4–7] AD can cause a significant impact on psychosocial functionality and patients' quality of life, affecting sleep, social interactions, and working productivity.[8,9] Moderate-to-severe AD may also carry a relevant economic burden.[10,11]

AD has a chronic remitting course. While in some patients the disease persists with minimal changes over time, in others, the clinical course is more fluctuating with periods of remission interrupted by acute exacerbations, also known as 'flares'.[2,12] Flares are an integral part of the AD disease course and are generally defined as disease worsening requiring escalation/intensification of treatment. The objective of AD management is to improve symptoms and establish long-term control by targeting flare prevention[3] and minimizing the frequency and severity of flare episodes. Despite both clinicians and AD patients being familiar with the concept of flares, a univocal definition and the most appropriate treatments remain uncertain.

In most of the previous works, either reviews or original research articles, flares were seen only as a side of a chronic disease. This review aims to focus on AD flares from definition to treatment, highlighting specific flare-related aspects that are lacking and identifying any necessary and urgent steps in this field to better manage AD.

Definition of flare

Due to the chronic-relapsing nature of AD, the ability to document disease flares is critical when evaluating treatment success. In addition, in clinical practice, the ability for patients to identify an event as a flare would also facilitate a better awareness of their disease course and improve communication with their clinician.

Table 1. Principal factors aggravating atopic dermatitis or triggering flares.

Endogenous	Environmental
Alteration of skin microbiota[16–26]	Exposure to allergens[27,28]
Skin barrier dysfunction[29–33]	Food allergy[34]
Dysregulation of cytokine production[29–31,34–37]	Hot and humid environment[38,39]
Stressful life events[38,40–47]	Dry and cold environment[38,48]
Hormonal changes (premenstrual phase, pregnancy)[49–54]	Sweating (physical exercise)[38]
	Sun exposure[55,56]
	Clothing with irritating fibers (wool)[57]

In clinical trials, flare/remission events are among the items used to evaluate the long-term control of AD, with 'time to first flare' the most commonly used endpoint in randomized controlled trials that included flare data.[13] A working group of AD experts identified, in 2014, a significant gap in methodologic research on the optimal instruments for defining disease flares in long-term AD trials.[12]

A systematic review of AD flare definitions, conducted on behalf of the international Harmonising Outcome Measures for Eczema (HOME) initiative, identified a wide variation in flare denotations from 26 prospective intervention studies published up to 14 February 2013.[14] This work highlighted the variety of flare definitions utilized, 22 in total, including the use of an arbitrary cut-off on an existing severity scale measured at sequential intervals by investigators, a patient-reported flare description, a composite definition involving multiple domains such as the perceived need for treatment and investigator's assessment, a behavioral meaning typically based around the need to modify therapy from a patient's or physician's perspective, and a symptoms-based expression. Notably, there were no validation studies of the flare definitions identified, limiting comparisons of clinical studies and the interpretation of outcomes.

In 2020, the European Task Force of Atopic Dermatitis (ETFAD) defined 'flare' as an 'Acute, clinically significant worsening of signs and symptoms of AD requiring therapeutic intervention'.[15]

Flare triggering factors

Flares may be aggravated or triggered by several factors, including endogenous and environmental factors (Table 1). These factors may induce or exacerbate pruritus and skin inflammation. The combination of the different triggers could potentially modulate the intensity and frequency of flares; thus, a proper evaluation of individual features and environmental exposure is critical in maintaining adequate disease control.

Endogenous factors

The molecular structure of the skin and complex interactions with skin microbiota (i.e. all microorganisms, bacteria, and fungi present on the surface of the skin) play a central role in the triggering of flares. Indeed, AD is associated with changes in the skin microbiota, and studies suggest that increased colonization by *Staphylococcus aureus*, alongside reductions in the diversity of skin bacteria, may be a relevant factor in disease exacerbation and possibly a direct cause of flares.[16–23]

Exploration of the prognostic value of intrinsic skin surface microbiome configurations has also identified a distinct dermotype in patients prone to severe itching and recurrent flares, with reduced abundance observed in several species that can prevent *S. aureus* overgrowth alongside enrichment of *Micrococcus luteus*, which can promote the proliferation and virulence of *S. aureus*.[17] Patients with AD have an increased risk of developing bacterial and viral skin infections, which can occur concomitantly with AD flares.[24,25]

Eczema herpeticum, caused by the herpes simplex virus and present in approximately 3% of patients with AD, is usually observed in the context of flare and favors AD skin lesions. Factors predisposing patients with AD to herpetic complications include, among others, a deficit in filaggrin, overexpression of Th2 cytokines, defective *versus* aberrant regulatory T cells, and dysbiosis of skin microbiota.[25] Predisposition to cutaneous viral infection should also be considered for AD onset and flare triggering. Indeed, molluscum contagiosum infection is associated with higher occurrence of AD flares in a subset of susceptible pediatric patients who were more likely to have a family history of AD. Whether the prevention of molluscum contagiosum infection may reduce flare onset still need to be elucidated.[26]

Moreover, sensitization to the fungal genus *Malassezia* spp., belonging to the skin microbiome, is associated with AD in predisposed individuals, likely eliciting IgE response, pro-inflammatory cytokines, and induction of auto-reactive T cells.[58]

Dysregulation of cytokine production plays a role in skin barrier dysfunction and may predispose patients with AD to increased skin inflammation and intense itch.[29,34–37] Intense scratch can generate skin lesions, leading to barrier disruption; this causes the release of a series of mediators and cytokines that in turn elicit the Th2 cell response.[29]

One of the structural components that regulate skin homeostasis is filaggrin.[30,31] The filaggrin protein aggregates with keratin within cells of the corneal layer of the skin conferring mechanical resistance to the tissue and forming a barrier to prevent loss of water and the penetration of external agents. Genetic mutations of the filaggrin gene (*FLG*), which cause protein loss-of-function, are recognized factors predisposing to AD due to the dysfunctional skin barrier. Nevertheless, *FLG* mutations are not solely responsible for the diminished filaggrin levels, suggesting the existence of a complex cross-talk between gene expression, skin microenvironment, external agents, and sustained inflammation.[29] Indeed, IL-4 also downregulates filaggrin, and other proteins involved in skin barrier formation and integrity such as loricrin and involucrin, via the JAK-STAT signaling pathway affecting epidermal permeability and allowing penetration by pathogens and allergens.[37]

Stress and psycho-neuro-immunologic factors impairing the epidermal barrier and immune response can also trigger flares.[40–44] Both acute and chronic stress have significant effects on immuno-pathology and immune-regulation, modulating immune response at both molecular and cellular levels, eventually increasing autoimmune and pro-inflammatory disorders such as AD.[45] The impact of psychological stress on skin diseases, including AD, comprises complex stress-induced skin reactions involving an intricate network of immune cells, hormones, and neurotransmitters, which may affect skin integrity, inflammation, and healing potential, and influence disease severity and the frequency of exacerbations.[46] In fact, besides the induction of inflammatory cytokines (IL-6, IL-1, IFN-γ), skin keratinocytes and fibroblasts can also secrete cortisol, adrenocorticotropic and corticotropin-releasing hormones, and signal peptides upon stress, actively taking part in onset and progression of flares.[46] Stressors, either internal (i.e. bacterial infections) or external (i.e. psychological), have also been reported to impair the skin barrier function favoring a T helper type 2 cell/allergic response and may induce AD flare.[40]

Other factors implicated in AD flare include hormonal influences. This concept is highlighted by clinical practice, as women frequently report the deterioration of AD during the premenstrual period.[49,50] Indeed, women in the premenstrual period have high estrogen concentrations, which promote Th2 response. The skin permeability barrier is impaired by progesterone, the hormone which dominates the luteal premenstrual phase. Dysregulation in the protease activity in the skin may also be relevant to the deterioration of the epidermal barrier in the premenstrual phase in women with AD.[51–53] The same hormonal influences may be involved in AD exacerbation or flares during pregnancy.[54]

Environmental factors

Environmental exposures (mechanic, chemical, or biological irritants) to respiratory allergens and food allergens may also induce flares.[1,3,4,59–61] Exposure to environmental factors in predisposed individuals may trigger AD flare by acting as pruritogens and irritants and can lead to the upregulation of inflammatory processes and deterioration of the skin barrier function.[61] In the context of

AD-associated inflammation, acute itch flares triggered by allergen exposure were dependent on immunoglobulin E (IgE), with a mouse model demonstrating the involvement of basophils in promoting acute itch flares.[27] Exacerbations were also demonstrated in adults with AD with known IgE sensitization to grass pollen following controlled exposure to airborne grass pollen in an environmental challenge chamber.[28]

The relationship between AD and food allergy is debatable, and evidence supporting allergen avoidance to improve disease severity is inconsistent.[34]

Intense acute itch exacerbations are characteristic of AD flares.[27,38] Triggers of itch in AD are heterogeneous, with the most commonly reported triggers being stress, sweating, weather change, dry air, and exposure to a hot and humid environment.[38] Indeed, the weather could be a relevant factor implicated in flare triggering. The impact of climatic conditions affects the clinical presentation of AD and may exacerbate AD flares.[38] Notably, specific itch triggers associated with the different seasons are heterogeneous, and their impact on individuals with AD may vary (i.e. predisposed individuals may be sensitive to cold temperature in winter or hot temperatures, sweating, and sunlight in summer). Across the geographically diverse United States, increased temperatures also predicted an increased likelihood of ambulatory AD office visits.[39] In the South, which has the hottest climate, there were substantially more AD office visits during summer, whereas none of the regional locations had clear evidence of an AD winter flare highlighting the relationship between season and temperature on the occurrence of flares.

A subset of patients with AD exhibit disease flare upon intense sun exposure. Photo-induced or photo-aggravated AD is not common but intense sun exposure can aggravate AD independent from the environmental temperature and humidity.[55,56]

Also, skin contact with irritating fibers (wool, large fibers textiles) can exacerbate pruritus and AD, especially in the context of a humid or dry environment.[57]

Clinical management of flares

Clinical management of AD should consider clinical, pathogenic, and individual variability and must target flare prevention.[4,15] The recommended treatment strategy for AD depends on disease severity, with particular attention to difficult-to-treat areas.[62] For the measurement of clinician-reported disease severity, the Scoring of Atopic Dermatitis (SCORAD) and the Eczema Area Severity Score (EASI) are among the most widely used tools.[63] Compared with the EASI, which describes skin disease, the SCORAD is a composite measure and assesses both objective signs and subjective symptoms (i.e. itch, sleeplessness). Systemic anti-inflammatory or immunosuppressive treatments are indicated for moderate-to-severe AD.[15,64,65]

For comprehensive details of AD treatment recommendations, refer to the consensus-based European guidelines for the treatment of AD in adults and children published in 2018[4,65] and the fourth edition of the ETFAD/European Academy of Dermatology and Venerology (EADV) Eczema Task Force Position Paper.[15] The management of flares is therapeutically challenging,[15] particularly when considering treatment-resistant presentations of AD.[66] Flare management, requiring effective short-term control of acute symptoms, should not compromise the overall management plan, which targets long-term safe control.

Regardless of disease severity, however, appropriate skincare must be adhered to, with the use of emollients and mild skin cleansers providing the basis for continued skincare and addressing the dysfunctional epidermal barrier with hydrating/lubricating topical treatment,[67] along with patient education programs and the avoidance of trigger factors.[4,15,65,68]

For visible skin lesions, topical anti-inflammatory treatments are based on corticosteroids and calcineurin inhibitors.[15] Topical steroids are the first-line anti-inflammatory treatment for acute flares and should be applied at the first sign of an acute flare and should not be spared.

If topical treatments have failed or are inadequate to control AD flares, other therapeutic options should be considered. The choice of systemic immunosuppressive treatment for flare management should be based mainly on the rapid onset of action.[15] Drugs targeting IL-4Rα or IL-13 inhibitors may need some time for an effective improvement: 4–6 weeks to reach most of

expected full response with drug targeting IL-4Rα[65] while, in some cases, IL-13 inhibitors may develop their full potential at a later time-point.[69] In contrast, JAK inhibitors are in general effective fast-acting drugs.[15,70]

Patients with acute flares should not be immediately treated with ultraviolet (UV) radiation but instead be subjected for a short time (days) to a standard regimen before considering UV therapy.[15] An exception is the use of UVA1, which consists of longer, non-erythemogenic UV wavelengths (340–400 nm) and may effectively manage flares.[4]

Systemic antihistamines may be used in acute flares, but evidence supporting their use in targeting itch is very weak, and their effects on AD-related itch and lesions are limited.[15] Topical antiseptics, as well as topical and systemic antibiotics, are recommended when clinical signs of bacterial infection (i.e. oozing and pustules) are associated with acute flares.[24] Secondary infections of lesions caused by fungal or viral agents (eczema herpeticum) should also be investigated early and treated promptly if present.

Prevention of flares

There is no universal strategy to minimize the recurrence of flares. The type of intervention should vary depending on the individual, frequency, severity, and sites of disease and can be either reactive (following the onset of the exacerbation) or proactive (with the aim of preventing a flare episode).[4,12,15,65]

A reactive approach to long-term AD management should include daily moisturizer to improve skin hydration and alleviate epidermal barrier dysfunction as part of a maintenance treatment plan, with anti-inflammatory therapies reintroduced following disease flares. Conversely, a proactive approach involves the long-term, intermittent application of topical corticosteroids or topical calcineurin inhibitors to previously and newly affected areas of skin alongside maintenance treatment with emollients to unaffected areas (Strength of recommendation = A; Level of evidence = I).[12]

For the prevention of AD flares, 'Continued use of either topical corticosteroids (1–2 times/week) or topical calcineurin inhibitors (2–3 times/week) after disease stabilization, to previously involved skin, is recommended to reduce subsequent flares or relapses' by a working group of recognized AD experts in 2014.[12] Similarly, ETFAD recommended proactive therapy with topical corticosteroids or topical calcineurin inhibitors in patients with moderate-to-severe AD.[15]

A proactive management strategy for AD consisting of long-term, intermittent application of topical corticosteroids was demonstrated as effective and well-tolerated in a randomized, investigator-blinded, controlled study in 30 patients with moderate-to-severe AD aged 3 months to 7 years.[71] In this study, patients were allocated to a proactive or reactive treatment group after undergoing an AD education program and followed for 12 months. Despite there being no significant between-treatment group differences in the average use of topical corticosteroids, the SCORAD index was significantly lower at the 12-month final visit in the proactive treatment group compared with the reactive treatment group ($p = 0.018$), with the proactive group showing significant improvement in quality-of-life measures ($p < 0.05$ *versus* baseline).

Although a proactive approach appears to be effective in preventing AD flares, it is unknown which class of topical anti-inflammatory therapy is more effective, highlighting the need for comparator studies. Overall, a proactive therapy results in a reduced barrier disruption in comparison with a daily application therapy, and a similar reduction of barrier disruption is obtained with the use of topical calcineurin inhibitors than with topical corticosteroids.[15] Indeed, topical corticosteroids and calcineurin inhibitors have been associated with reducing pruritus, with topical calcineurin inhibitors more effective than topical corticosteroids.[15] Furthermore, the optimal interval of scheduled intermittent use (i.e. application twice weekly, three times per week, or weekly on two consecutive days) and whether topical anti-inflammatory is more effective if applied once *versus* twice daily is unclear.[12] There is no evidence of harm when topical corticosteroids are used intermittently 'as required' to treat flares or 'weekend therapy' to prevent flares. However, long-term safety data are limited.[72] For topical calcineurin inhibitors, whether continued daily use is more efficacious than scheduled, intermittent dosing is unknown.

Structured educational programs for both patients[68] and caregivers (Strength of recommendation = A; Level of evidence = I) may facilitate a better understanding of the disease and management goals, including the appropriate use of therapies, and improve treatment adherence and reduce misconceptions.[12] Notably, long-term beneficial effects, including improved coping behavior, quality-of-life parameters, and overall disease severity, were demonstrated in a multicenter, randomized, controlled study led by a multidisciplinary team in an outpatient setting that compared 129 patients assigned to a patient education program for adults with AD with 104 control patients.[68]

When using phototherapy to treat AD, co-medication with topical corticosteroids and emollients should be used to reduce the likelihood of flares.[4,15] In selected cases, the avoidance of relevant allergens such as food allergens, airborne allergens (i.e. house dust mites, pollen), contact allergens, and animal epithelia may be crucial as exposure may lead to exacerbation of AD.[4,15]

Conclusion

Flares are an integral component of the AD course in many patients. However, current knowledge on specific flare-related aspects is limited, requiring further investigations. A better understanding of the role of the skin microbiota (i.e. colonization by *S. aureus*, loss of bacterial diversity of skin) in acute flares is paramount due to its impact on disease severity and recurrence. Numerous flare triggering factors are already known, but questions remain as to the cause of alterations to the skin microbiota resulting in the onset of a flare, the critical role of environmental factors in the onset of AD and disease flares, and whether environmental and food allergens are universal in inducing flares.

The optimal treatment for flare prevention in patients with AD is also uncertain, and the role of the reactive and proactive approaches needs to be further explored for flares, considering the complexity of clinical manifestations, in order to have better long-term control of the acute exacerbations and extend the time to relapse.

In AD clinical trials, flares represent a unique aspect of long-term AD control and should be detailed alongside composite measures. In addition, further research is warranted on how best to capture data on AD flare in real time and whether patient-reported outcome measures are superior for defining flares *versus* investigator-lead assessment at scheduled clinical visits.

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