Guidelines review on atopic dermatitis management

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Practice Points

- Emollients are the mainstay of atopic dermatitis maintenance management.
- Topical corticosteroids are the first choice therapy during flares.
- Topical calcineurin inhibitors may be considered the first-line treatments in certain areas such as the face and flexures.
- Cyclosporin is the first-line immunosuppressant in severe atopic dermatitis, although azathioprine and mycophenolate mofetil are useful off-label alternatives.
- Guidelines facilitate the decision to start certain treatments, although individualized management should always be taken into account.

SUMMARY Many therapeutic options are available to manage atopic dermatitis, reflecting the absence of an effective treatment for this condition. Several guidelines have been published recently concerning the treatment of atopic dermatitis. The aim of these publications was to offer standardized strategies in the management of these patients. However, many recommendations lack quality scientific data and are based on clinical experience. Thus, current guidelines provide the best data available to lead physicians to decide what is best for their patients.

Atopic dermatitis (AD) is a chronic inflammatory disease characterized by pruritus and relapsing episodes of eczema, especially in the flexural areas and the face. Typically, onset of the disease is before the age of 5 years, although some cases might start during adulthood. The etiopathophysiology of the disease is multifactorial, involving genetic aspects, environmental triggers and immunologically altered pathways. Taking all of these things into consideration, the therapeutic approach towards AD has a wide range of treatments and strategies, which in fact reflect the absence of a highly effective treatment for AD. Bearing that in mind, many guidelines have been published by the most important dermatological societies in order to offer an individualized treatment for each patient by using a standardized management of AD.

However, scientific evidence for many of the treatments used in AD is poor because of

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the lack of randomized clinical trials. This is a frequent situation in most dermatological therapies, such as corticosteroids, which are in fact old treatments that were developed before the clinical trials era.

Although there is no global consensus, the general therapeutic approach presented in the different guidelines is quite similar, including a ladder treatment strategy that starts with supportive treatment and avoidance of AD triggers, is followed by topical therapies such as topical corticosteroids (TCS) or topical calcineurin inhibitors (TCIs), and is finally completed by a broad group of treatments that includes phototherapy, immunosuppressants and other systemic therapies.

The aim of this article is to compare the most important publications in English on AD management, especially the latest guidelines published. We therefore decided to review the latest European guidelines for treatment of AD published in 2012 [1,2], the European Task Force on Atopic Dermatitis guidelines [3], the British Guidelines [4], the American Academy of Dermatology guidelines [5] and the Japanese Dermatological Association guidelines [6] by trying to find the common points in the management of AD.

Emollients & prevention strategies

Emollients are still considered the mainstay of AD maintenance management in all the recent guidelines, and should be applied continuously to prevent flares. However, some authors differ on the usefulness of emollients during the acute phase. In the European guidelines, it is not recommended to use emollients during the acute flare as it may be irritating. Instead, these authors suggest using a greasier vehicle of the topical treatment such as an ointment, as well as using emollients after the application of topical therapy. However, the British, American and Japanese guidelines advocate for the use of emollients during the acute flare, even 10–15 min before the application of topical treatments [4–6]. In our opinion, we support the avoidance of emollients during the acute phase in active eczema plaques, as moisturizers such as urea penetrate the inflamed skin and might worsen the pruritus, not permitting the AD flare to be overcome. However, emollients can be applied to apparently healthy skin in order to prevent the appearance of a new eczematous lesion.

Other prevention strategies consist of avoidance of triggers such as long baths, acid soaps, wool and certain allergens such as dust mites or specific foods. However, performing allergy tests on atopic patients is not universally recommended as there may be different opinions on how to interpret the results between allergologists, pediatricians or dermatologists. In our opinion positive allergy tests in atopic patients should be interpretted carefully as they normally reflect a hyper-reactive skin to certain stimuli such as cow's milk, wheat or hen's eggs, rather than a real food allergy.

Topical therapies

TCS are considered the main therapy during the acute flares by all of the guidelines. However, they cannot be used continuously on a daily basis as they might produce cutaneous atrophy, telangiectasias, striae and even systemic effects. Moreover, children may tolerate the application of TCS poorly, especially when extensive areas are affected. Therefore, a reasonably safe and efficacious second-line strategy is the 'wet-wrap' technique. This consists of applying a wet dressing before the application of TCS, or even applying emollients or diluted corticosteroids to the patient's skin, and afterwards dressing the child with the wet-wrap. This relieves the oozing associated with eczema, as well as increasing the absorption of TCS [7].

Alternative treatments to TCS are TCIs such as tacrolimus ointment and pimecrolimus cream. These treatments are considered second-line therapies, although they can be considered to be first-line drugs in certain areas such as the face, flexures and genital area, as they do not produce atrophy of the skin.

A novel approach in the topical treatment of AD that is considered useful, especially in the latest European guidelines, is proactive treatment, a term that was first introduced in 2008 [8]. This consists of the application of TCS or TCI twice weekly in the locations frequently affected by eczema, although the skin appears to be healthy. This strategy reduces the number of flares by considering the atopic skin to always have some degree of inflammation [9]. In the authors' view the proactive approach is one of the key points in the success of the symptomatic control of AD. Furthermore, we consider the application of a TCI preferable to avoid any adverse effect of the steroids.

Antipruritic therapy

Traditional antipruritic therapies with antihistamines are poorly effective in AD, suggesting that histamine has little relevance in the pruritic pathway of this disease [10]. However, some guidelines, such as the British, European and American, suggest that sedative antihistamines might be useful in order to facilitate sleep at night, which may be impaired due to itching. Nevertheless, the Japanese guidelines support both sedative and nonsedative antihistamines. In the authors' opinion, antihistamines show little effect in the atopic pruritus, and therefore should only be used as sedative medications in order to facilitate sleep at night.

Antimicrobial therapy

Although *Staphylococcus aureus* is not considered part of the healthy cutaneous flora, it colonizes the skin in over 90% of AD patients [11]. More than two-thirds of *S. aureus* found in the skin of AD patients secrete exotoxins that may act as superantigens, worsening eczema flares [12]. Other microorganisms that may produce secondary skin infections are *Malassezzia* yeasts, dermatophytes, herpes simplex virus, and β-hemolytic streptococci [13], also leading to worsening of the eczema. This results in a completely different approach that involves decolonization and treatment of active cutaneous infections.

All recent guidelines advocate the use of antibiotics if there is an active bacterial infection, especially because certain microorganisms may exacerbate or worsen a flare. In these patients antibiotics should be used to prevent flares. Moreover, treating fungal or viral infections is equally recommended. Nevertheless, some authors recommend the use of both anti-inflammatory drugs and antibiotics during the flares in order to reduce its severity by suppressing the release of superantigens [14].

Nevertheless, controversy has been raised as to whether it is necessary to decolonize these patients between the flares with antiseptics or other antimicrobials. Some authors support the use of antiseptics such as bleach baths plus intranasal application of mupirocin ointment between the flares, suggesting that this may reduce the severity of eczema [15]. However, most authors do not support decolonization of *S. aureus* with antibacterials because of the lack of effect on clinical improvement and an increased risk of resistances [16]. Moreover, due to the ubiquitous nature of *S. aureus*, frequent recolonization may occur, and therefore little benefit is obtained from decolonization [17].

In the authors' opinion, antibiotics should be used in acute flares in order to reduce the amount of staphilococci and thereby reduce superantigen stimulation, which may worsen the eczema. Obviously, treating impetiginized areas is mandatory, even in the absence of a flare. Nevertheless, we do not recommend the use of antiseptics between the flares in order to decolonize patients, as we believe they may have little therapeutic effect.

Phototherapy

It is well known that the cutaneous lesions of atopic patients improve during summer with sun exposure, and therefore, artificial UV radiation has been used to treat AD. All of the major guidelines support the use of phototherapy for AD, although it is considered a second-line therapy. In addition, the European guidelines support the use of phototherapy in chronic lichenified lesions in patients with moderate AD, not during the acute flare. However, in the authors' opinion phototherapy is not as useful as is stated in the previous guidelines, especially because of its increased carcinogenic effect and inconvenience of performing two to three sessions per week, disturbing the daily studies or job of patients. Moreover, phototherapy should not be used in patients younger than 12 years old, narrowing phototherapy's usefulness. We consider other effective therapies such as systemic immunosuppressants to be better alternatives to phototherapy in patients with refractory moderate/severe AD.

Systemic immunosuppressants

Several immunosuppressants can be used to treat moderate-to-severe AD that does not respond to other therapies. However, only a few can be recommended with a strong level of evidence due to the lack of randomized clinical trials. One example of these is systemic corticosteroids, which have been extensively used to treat acute flares, despite the absence of scientific evidence. Most of the guidelines highlight the fact that oral corticosteroids can be used in short pulses to control acute flares, but should be avoided on a long-term basis due to their side effects and loss of response.

Conversely, cyclosporine is a treatment that has been extensively studied and is licensed in Europe for treating AD. This systemic calcineurin inhibitor has been proven to be an effective and fast therapy to control moderate-to-severe AD. It is recommended by most of the guidelines, although its use has to be limited to acute flares because of its side effects, especially hypertension and renal toxicity. Nevertheless, some studies have shown long-term efficacy and safety for up to 4 years [18], although most guidelines do not recommend using it for more than 2 years. Moreover, most authors recommend a very slow, sparing dose in order to avoid a prompt relapse.

Azathioprine has been used for many years to treat AD with good results, although its effect is slower than cyclosporine. European guidelines refer to azathioprine as an off-label alternative to cyclosporin when the latter is ineffective. However, the American and Japanese guidelines do not support the use of this therapy, possibly because they are older and very little data had been published concerning its use in AD. An important aspect to be taken into account is the determination of thiopurine methyltransferase, which should be performed before the use of azathioprine. This allows dose adjustment in order to avoid myeloid toxicity. When adjusted to thiopurine methyltransferase, azathioprine is a safe treatment that can be used for long periods. However, a limiting aspect of azathioprine is that the response usually starts after 3 or 4 weeks, which makes this treatment often unsuitable when facing an acute flare.

Another valid alternative for treating severe AD is mycophenolate mofetil and its salt, mycophenolate sodium. Both have some of the best safety profiles with good efficacy, although its effect is not as fast as cyclosporin, as with azathioprine. Therefore, concomitant use initially with oral corticosteroids may be advisable [17]. Only a few guidelines recommend these medications, mainly because of the lack of sufficient data. Nevertheless, mycophenolate sodium has been studied in a randomized controlled clinical trial in order to assess its efficacy [19], showing similar results to cyclosporin with fewer adverse events. The authors support the use of these treatments especially in patients with refractory AD that may need long periods of therapy.

Methotrexate has similar effects to azathioprine, although blood count abnormalities may be more frequent with the latter [20]. Only European guidelines recommend methotrexate, although recent US publications may propose this therapy as a good option for maintenance therapy in severe AD, once the flare has been controlled [17].

In our view, methotrexate may be used in treating AD, although we prefer azathioprine or mycophenolate mofetil due to its better safety profiles. Moreover, in our personal experience, we achieve better results with azathioprine, even in patients who are naive to other immunosuppressants such as cyclosporine. Nevertheless, data from clinical trials suggest that mycophenolate mofetil has similar efficacy but better tolerability than azathioprine. Hence, the decision on whether to choose one treatment or another depends on other factors such as one's experience or costs.

Other therapies

Biological treatment with monoclonal antibodies has been reported to be useful in some patients with severe AD. However, only the continental European guidelines refer to these treatments as possible therapeutic options, although no biological treatment is yet supported. Furthermore, data from randomized clinical trials is lacking and information referring to its usefulness is limited.

T lymphocytes are altered in AD, and therefore some biologic treatments focusing on this response have been used with good results, for example infliximab, etanercept, alefacept and, recently, ustekinumab [21]. Furthermore, elevated IgE levels are found in AD. Thus, some reports concerning the anti-IgE antibody omalizumab have been published, although results are poor. From the authors' point of view, the use of biologics may be useful in the future in AD but there is currently not enough data to recommend its use. However, a better understanding of the disease is fundamental to correctly use the present therapies or develop new targeted treatments.

Alternative medicine, herbal therapies and acupuncture are other strategies that have been studied, although they are only recommended in the Japanese guidelines. From our point of view, there is not enough data to recommend the use of these therapies, and caution may be advised on certain treatments such as Chinese herbs, which may produce renal [22] and hepatic impairment [23]. Nevertheless some of these strategies may

be beneficial in some patients provided that they may increase their relaxation and comfort.

Training parents, patients and relatives on how to use the topical treatments or teaching how to prevent triggers is recommended by most guidelines. An excellent evidence-based method to do so is the creation of 'eczema schools' [24]. We also support the use of these strategies as a better understanding of the disease and how to correctly apply the treatment greatly reduces the number of flares.

Conclusion

The management of AD is complex, as many therapies are available to treat this disease. As a result, this may indicate that none of these treatments are fully efficient. Although guidelines of the main dermatological societies have been published, a global consensus concerning the management of AD is lacking. The authors tried to compare the main guidelines to date, adding our professional experience.

First, the authors consider the mainstay of treatment for mild-to-moderate AD to be TCS, but TCI can also be used as a first-line therapy, and the authors prefer to treat certain areas such as folds, genitalia and the face with TCI. Furthermore, proactive treatment is fundamental to prevent flares, and the authors suggest the use of TCI twice weekly in the most frequently affected areas. Moreover, emollients should be used in noneczematous areas, even during the acute flare and during maintenance, but should be avoided in the inflammatory areas.

In the authors' opinion, cyclosporin is the first-line therapy of choice to treat severe AD. Nevertheless, the authors suggest that azathioprine or mycophenolate mofetil can be used as first-line immunosuppressants because of their good results and the possibility of using this treatment during longer periods.

To summarize, guidelines facilitate the decision on whether to start certain treatments, although information coming from randomized controlled trials is limited. Therefore, an individualized management strategy should always be taken into account in order to best treat atopic patients.

Future perspective

This review leads to the belief that proactive treatment, especially in childhood, could be very useful to avoid flares and promote general improvement for adulthood.

Furthermore, the future of new biological treatments targeting the immunological defects of AD could be very interesting in the near future.

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- ▪ of interest
- ▪▪ of considerable interest

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▪▪ **Includes the latest European guidelines for the management of atopic dermatitis (AD), which are the most extensive and evidence-based guidelines on this subject.**

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