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Atopic Dermatitis Guideline. Position Paper from the Latin American Society of Allergy, Asthma and Immunology

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ABSTRACT

As in other regions, the incidence of atopic dermatitis in Latin America has been increasing in recent years. Although there are several clinical guidelines, many of their recommendations cannot be universal since they depend on the characteristics of each region. Thus, we decided to create a consensus guideline on atopic dermatitis applicable in Latin America and other tropical regions, taking into account socio-economic, geographical, cultural and health care system characteristics. The Latin American Society of Allergy Asthma and Immunology (SLAAI) conducted a systematic search for articles related to the pathophysiology, diagnosis and treatment of dermatitis using various electronic resources such as Google, Pubmed, EMBASE (Ovid) and Cochrane data base. We have also looked for all published articles in Latin America on the subject using LILACS (Latin American and Caribbean Literature on Health Sciences) database. Each section was reviewed by at least two members of the committee, and the final version was subsequently approved by all of them, using the Delphi methodology for consensus building. Afterward, the final document was shared for external evaluation with physicians, specialists (allergists, dermatologists and pediatricians), patients and academic institutions such as universities and scientific societies related to the topic. All recommendations made by these groups were taken into account for the final drafting of the document. There are few original studies conducted in Latin America about dermatitis; however, we were able to create a practical guideline for Latin America taking into account the particularities of the region. Moreover, the integral management was highlighted including many of the recommendations from different participants in the health care of this disease (patients, families, primary care physicians and specialists). This practical guide presents a concise approach to the diagnosis and management of atopic dermatitis that can be helpful for medical staff, patients and their families in Latin America.

Key words: allergy, allergen, atopy, dermatitis, eczema.

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Guía de dermatitis atópica. Consenso de la Sociedad Latinoamericana de Alergia, Asma e Inmunología

RESUMEN

La incidencia de dermatitis atópica en Latinoamérica muestra un incremento constante, si bien existen muchas guías clínicas de dermatitis

atópica, muchas de las recomendaciones no pueden ser válidas de manera universal debido a las particularidades de cada región. Por ello, nos propusimos crear una guía de consenso de dermatitis atópica válida para Latinoamérica y otras regiones tropicales, que tome en cuenta las características socioeconómicas, geográficas, culturales y de los sistemas de salud. La Sociedad Latinoamericana de Alergia, Asma e Inmunología (SLAAI) realizó una búsqueda sistemática de artículos relacionados con la fisiopatología, el diagnóstico y el tratamiento de la dermatitis atópica usando diversas fuentes electrónicas, como Google, Pubmed, EMBASE (Ovid) y Cochrane. También realizamos una búsqueda extensa de las publicaciones realizadas en Latinoamérica utilizando el buscador LILACS (Literatura Latinoamericana y del Caribe en Ciencias de la Salud). Cada sección fue revisada por al menos dos miembros del comité y luego una versión final fue aprobada por todos los participantes, utilizando la metodología Delphi para la construcción de consensos. Finalmente, el documento final fue compartido para la evaluación externa por médicos, otros especialistas (alergólogos, dermatólogos, pediatras), pacientes e instituciones académicas, como universidades y sociedades científicas relacionadas con el tema. Todas las recomendaciones dadas por estos grupos se tomaron en cuenta y se incluyeron en la versión final del documento. Existen pocos estudios realizados en Latinoamérica acerca de dermatitis; sin embargo, fue posible crear una guía que considera las particularidades de la región tropical. Además, destacó el tratamiento integral porque se consideraron muchas de las recomendaciones ofrecidas por los diferentes participantes en el tratamiento de esta enfermedad (pacientes, familiares, médicos de atención primaria, especialistas).

Esta guía práctica expone una aproximación concisa del diagnóstico y tratamiento de la dermatitis atópica que puede ser útil para el personal médico de todos los niveles, el paciente y su familia en Latinoamérica.

Palabras clave: alergia, alergeno, atopia, dermatitis, eccema.

BACKGROUND

Atopic dermatitis affects a large part of the population, particularly children under 5 years. It usually precedes the development of other allergic diseases such as food allergy, asthma, rhinitis and/or conjunctivitis, so it is considered an important risk factor for these diseases. Therefore, the evaluation and management of atopic dermatitis should be comprehensive and must include all participants in the process of health care: patients, families and health care system.

Although there are excellent guidelines that offer an appropriate approach for the management of this disease, the environmental characteristics of the tropics and subtropics make it necessary to create a guideline addressed to the particularities of atopic dermatitis in Latin America. This guideline is not intended to restrict the treating physician about how to make their management approach. Since each patient must receive a personalized treatment, the recommendations presented here may not be appropriate for all patients but offer a starting point for management based on current scientific evidence.

METHODOLOGY

The committee of atopic dermatitis of the Latin American Society of Allergy Asthma and Immunology (SLAAI) developed this guideline. It was conceived because of the necessity to create a guide that takes into account the particular aspects of atopic dermatitis in Latin America and in tropical and subtropical regions. As a starting point, the committee organized a table of contents that was divided into sections, reviewed by at least two committee members and then discussed by all the staff. The points regarding the diagnosis and management were defined by vote using the Delphi method. Each management section concludes with a summary of the topic, which includes the strength of the recommendation and a statement of the group based on current evidence in Latin America.

To facilitate understanding by health care staff and patients, recommendations on the diagnosis and treatment were divided into "strong", "moderate" or "weak" according to the GRADE system (Grading of Recommendations Assessment, Development and Evaluation). We classified as "strong recommendation" when the opinion of the working group was supported by scientific evidence of high quality; "moderate recommendation" when the opinion of the group was homogeneous (greater than 90%), but the scientific evidence was not of high quality; and "weak recommendation" when the opinion of the group was heterogeneous and/or the evidence was of poor quality (Table 1).

This guideline had a process of external validation to assess the clarity of the concepts and their applicability. The manuscript was presented to different allergists, dermatologists, general practitioners, allergy and dermatology residents, patients and family groups. External recommendations were then discussed again by the members of the Committee and then included in the manuscript.

DEFINITIONS

For most of the terms used in this article, we use the nomenclature proposed by the World Allergy Organization (WAO) in 2004.[1] According to the recommendation of the WAO, the general term for a local inflammation of the skin should be "dermatitis", while proposing the term "eczema" to replace the term previously used as "syndrome eczema/dermatitis".[1] They also recommend limiting the use of the term "atopic eczema" when a mediation IgE is demonstrated in the pathophysiology of the disease, and "non-atopic eczema" when it is discarded. While confirmatory immunological studies are done, they recommend only using the term eczema.

However, in many countries of Latin America the term "dermatitis" is used as equivalent to "eczema", so in this guideline they are used a common term.[2-4]

EPIDEMIOLOGY

Atopic dermatitis is the most common skin allergic disease, affecting 1% to 20% of population.[5] It has an onset in 80% of cases in children under 2 years of age; no significant differences between genders in the first years of life, but it is most frequent in women (60%) than in men (40%) after 6 years.[6,7] Atopic dermatitis usually tends to remission symptoms before 5 years in 40% to 80% of patients[8,9] and in 60% to 90% at 15 years of age. This disease has been recognized as an important risk factor for the development of other allergic diseases such as food allergy, rhinitis and asthma.[10,11]

Kemp et al.[12] observed that stress and psychiatric problems in patients with moderate to severe dermatitis were higher than those in patients

Table 1. Strength of recommendation

Recommendation level assigned by the Working Group to interventions	Delphi method (recommended or not recommended intervention)	GRADE clasification system	
		Category of evidence according to GRADE system	Strength of recommendation
Strong	> 90% of the voting agreement	Ia: evidence from meta-analysis of randomized controlled studies. Ib: evidence from at least one controlled study. IIa: evidence from a non-randomized controlled study.	A: based on evidence from category I. B: based on evidence from category II or extrapolated recommendation from category I
Moderate	70 to 89% of the voting agreement	IIb: evidence from at least one quasi-experimental study. III: evidence from nonexperimental descriptive study (example comparative studies)	C: based on category III evidence or recommendations from evidence class I or II
Weak	50 to 69% of the voting agreement	IV: evidence from opinions or clinical experience of experts in the field	D: based on category IV evidence or evidence from recommendations from category I, II, III

with diabetes mellitus. In the 90s, Lapidus et al. estimated that the United States spent 365 million dollars annually to treat atopic dermatitis, including pharmacological management only.[13] A British study that included payment for physician visits, drug treatment (no skin hydration) and the loss of working days, estimated that the economic costs were 700 million per year.[14]

Differences in the prevalence and the incidence of atopic dermatitis may be due to many reasons, including the diagnostic criteria selected in each study.[15] However, some international approaches using the same diagnostic tools have shown significant regional differences, perhaps due to genetic and environmental factors.[16] The ISAAC study (International Study of Asthma and Allergies in Childhood)[5,17] defined the presence of dermatitis using the Hanifin and Rajka diagnostic criteria across surveys completed by the participants. In the phase three of that study, several centers from Latin American countries were included. It was observed that among children aged 6-7 years, the presence of "actual eczema" varied from 0.9% in Jodhpur (India) to 22.5% in Quito (Ecuador). Among children between 13-14 years, the prevalence ranged from 0.2% in Tibet (China) to 24.6% in Barranquilla (Colombia). In both age groups, the prevalence in Latin America was higher when compared with other countries, with values over 15% in several centers. This higher prevalence could have multiple causes including observational bias, but it may also reflects that may be some Latin American factors as high exposure to mites, the high genetic heterogeneity, have an important effect in the development of dermatitis.

PATHOPHYSIOLOGY

Atopic dermatitis is a complex and multifactorial disease. It is currently known that not only Th2 and IgE-mediated hypersensitivity are involved, but also the Th1 and even an autoimmune response.[4,18] Multiple genes may be involved in its development, conferring risk or protection between populations.[19] Several genes from the immune system has been involved (STAT-6, RANTES, TGF-beta);[20-22] Filaggrin gene is located in the locus 1q21. This is a gene that encodes

a protein of the same name, whose metabolites are involved in the formation of the "natural moisturizing factor".[23] Several polymorphisms associated with non-expression of this gene have been strongly associated with the development of atopic dermatitis: 30% of patients with dermatitis have one of these polymorphisms, but 60% of all cases are concentrated in patients with severe presentations (SCORAD >40). However, as mentioned above, this disease is multifactorial and even though these mutations give a predisposition, there is not demonstrated a direct cause of the disease by the presence of these polymorphisms, and 15% of the population without dermatitis or other allergic diseases have it.[24]

The development of atopic and non-atopic dermatitis involves several mechanisms which can act together generating different pathways. However, two main points are present in all phenotypes: *1)* an alteration of the integrity of the skin barrier and *2)* an immune inflammatory process. In search of clarity, we comment those points separately.

Alteration of the skin barrier

The skin is a physical barrier that prevents the entry of multiple agents as organic and inorganic contaminants. Alterations in proteins or cells involved in the barrier function carry the entry of microorganisms, irritants and allergens, leading to a neuroimmune-inflammatory response with the consequent development of symptoms such as itching. It has been shown that patients with dermatitis have higher blood levels of substance P, nerve growth factor (NGF) and vasoactive intestinal polypeptide (VIP), and increased exposure and stimulation of Malpighian receptors.[25] It has been observed that the skin damage persists caused by an inflammatory cycle difficult to break:[26] skin disorders increase transepidermal water loss and inflammation, which in turn stimulates scratching, increasing skin damage and inflammation which in turn causes more xerosis. There is an increased infiltration of T lymphocytes, eosinophils, macrophages and Langerhans cells in patients with dermatitis, even in apparently healthy skin.[27]

Keratinocytes play a major role in the innate immune response by producing antimicrobial peptides and preventing the invasion of microbes in the subcutaneous tissues.[28] It has been observed that in a significant number of patients with atopic dermatitis, there is an accelerated apoptosis of keratinocytes, which favors the colonization of bacteria, including *Staphylococcus aureus* (*S. aureus*) that increases inflammation, either by the generation of an IgE response against the proteins or producing super antigens recognized by T cells.[29] The overgrowth of *S. aureus* or any other bacteria at the cutaneous level leads to the loss of balance of the microbiota, thereby disrupting natural barrier.

Immunological alterations

Several skin cells, including Langerhans cells, myeloid dendritic cells and inflammatory dendritic epidermal cells which, similar to innate cells, are in more quantity in patients with atopic dermatitis, especially during exacerbations.[30] These antigen-presenting cells, especially Langerhans cells, favor an inflammatory response and present allergens to immature T lymphocytes (both CD4 + and CD8 +) which are activated and become mature T cells specific for the allergen that generated activation. These lymphocytes may be Th1 or Th2;[31,32] Th2 lymphocytes stimulate activation of B lymphocytes producing immunoglobulin E, which attaches to its high affinity receptors on the membrane of multiple cells located at skin level as basophils and mast cells.[33] IgE may also be bonded to other effector cells at the level of the peripheral circulation as eosinophils.[34] When a new allergen exposure occurs, this re-

sort Allergen/IgE/receptor can lead to a quickly degranulation of basophils and mast cells[35] and to a production of chemokines, which promote inflammation and migration of new mature T lymphocytes, beginning the process again. This inflammatory process could be extended to other systems and this is why dermatitis is strongly associated with asthma, rhinitis and conjunctivitis.[36] It has been demonstrated that a group of patients with dermatitis may have an autoimmune response generated by cross-reactivity between allergens and endogenous proteins from the patient;[37,38] this response appears to be associated with more severe symptoms.

RISK FACTORS

The increasing knowledge of the mechanisms of atopic dermatitis and the investigation over several birth cohorts, have allowed the identification of various factors that may be influencing directly or indirectly in its development. These factors and their clinical impact vary according to each region. Among the most strongly associated factors are family history of atopy, or personal development of asthma.[39,40]

The ISAAC study in Europe suggests that the urban environment,[41] early sensitization to food and aeroallergens, high socioeconomic strata and few family members[7,41] are factors that increase the risk of developing atopic dermatitis. These factors also appear to be important in Latin America, but cohort studies conducted in this area also indicate that additional factors may play a protective role or a risk.

The FRAAT (Risk Factors for Asthma and Atopy in the Tropics) birth cohort consists of 326 children from the lowest socioeconomic strata (lower income of $200 per month) of Cartagena (Colombia), and who have strong African ancestry.[42] In this cohort, none of the children at age of three had developed atopic dermatitis, suggesting that genetic inheritance and low sanitary conditions with greater exposure to endotoxin and other substances inherent to low economical income would be protective factors. These results are in stark contrast with data from the ISAAC study in Latin America, especially in the city of Barranquilla, which is located very near to Cartagena. Both cities share similar geographical conditions, but the frequency of dermatitis in Barranquilla is one of the highest in Latin America. Given that the ISAAC study carried out the survey among families with children over 6 years, one possibility is that in some cities in Latin America, the onset of dermatitis is later (> 3 years) similar to that found in some European countries.[6] The African heritage as a protective factor is supported when compared FRAAT cohort with a population of 600 children between 1 and 5 years in Buenos Aires (Argentina).[43] Just as in the FRAAT cohort, the cohort in Buenos Aires was of low economical income population, but it was predominantly white and the prevalence of dermatitis was about 40% contrasting with 0% in the cohort of Cartagena.

The concept of "atopic march" and the "hygiene hypothesis" must also be interpreted in a particular way in Latin America. The rapid urbanization in Latin American countries, economic development, the improvement of water quality, health coverage and the increasing adoption of Western lifestyle with consequent changes in diet, are important factors occurring in the region,[44] raising the possibility that these important changes can have unexpected consequences favoring the development of allergic diseases. The immune mechanism originally proposed to explain the high impact of allergies in developed countries was the decreasing number of infections by bacteria and virus, with the consequence of less Th1 stimulation, favoring the development of Th2 response. In Latin American populations, helminthes infection appears to have an important role in sensitization and some respiratory

allergies. That has been demonstrated in some cohorts in Brazil, Colombia and Ecuador.[45-47] Because helminthes are not currently a major problem in most European countries and the United States, the impact of helminthes infection in dermatitis should be studied as a particular factor in Latin America.

DIAGNOSIS

The diagnosis of atopic dermatitis is based on a set of clinical symptoms and signs, but to date, there is not a definitive diagnostic test. The presence of pruritus is an universal symptom in patients with dermatitis who also have eczematous lesions with periods of exacerbation and control. The distribution of eczema can change with time. In children under 2 years the involvement of the face and the extensor regions is usually more common that in the elderly, where the involvement of the folds becomes more relevant; however, these distribution is not exclusive to each group. The major criteria of Hanifin and Rafka[48] proposed over 30 years ago, adequately summarized the main criteria to be taken into account when evaluating a patient with suspected atopic dermatitis. All proposals that emerged posteriorly as Williams criteria are based in original Hanifin and Rafka criteria:[49] *1)* pruritus, *2)* distribution and typical morphology (facial involvement and extension areas in children, and in the areas of flexion in adults), *3)* chronic or recurrent symptoms and *4)* personal or family history of asthma, rhinitis and/or dermatitis

For diagnosis, it is essential the presence of pruritus and at least two of the other criteria. Hanifin and Rafka proposed to support the diagnosis in the presence of at least three "minor criteria". Minor criteria consist of some nonspecific signs

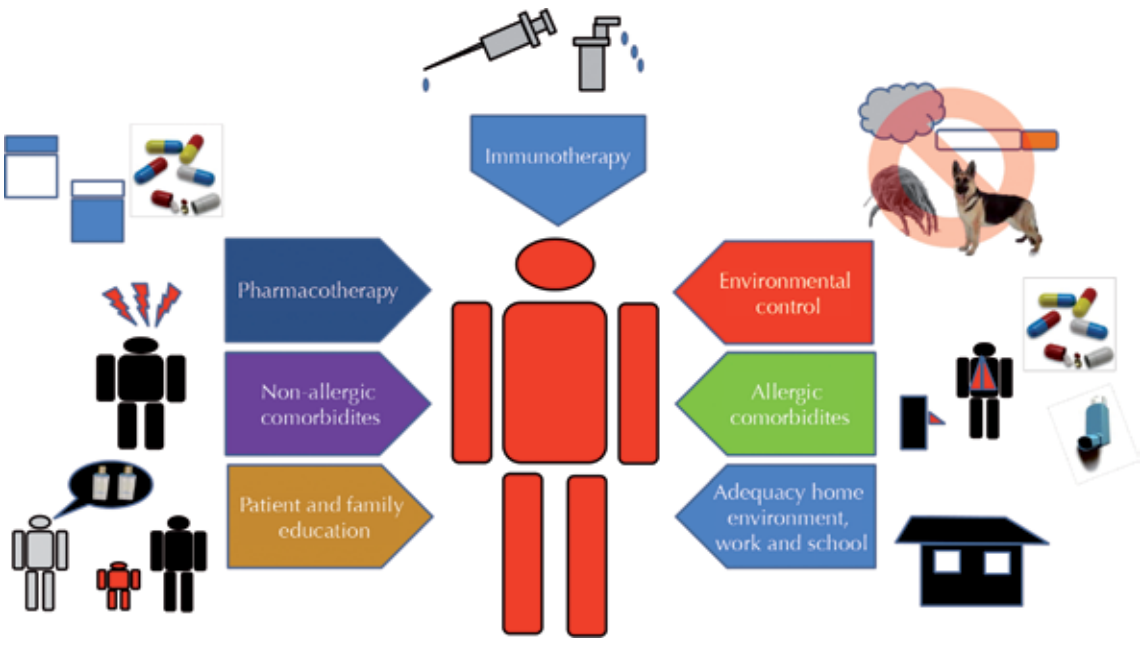

Figure 1. Integral management. The patient with dermatitis requires comprehensive management including education for both the patient and their family as guidance at work and/or school. Education should be aimed at improving control allergic and non-allergic comorbidities.

and symptoms which suggest allergy, like xerosis, pityriasis alba, cheilitis, follicular hyperkeratosis, white dermatographism, ichthyosis, high total IgE, conjunctivitis, tendency to skin infections, facial erythema, Dennie Morgan bifold, sensitization to food, contact dermatitis and seborrheic dermatitis, among others.

Severity

Classifying the patients according to the severity and intensity of symptoms allows evaluating in an appropriate and effective manner the response to treatment. Several tests have been developed for this purpose and have been validated in different populations.[50] Among the most frequently used are the SCORAD (Severity Scoring of Atopic Dermatitis), the objective SCORAD, EASI (Eczema Area and Severity Index), and the POEM (Patient-Oriented Eczema Measure).[51,52] The full version of any of these scales and its usage can be obtained in the references cited, and there are several applications to computers, mobile phones and tablets that allow a quick and easy access. In these tests, the severity of dermatitis is basically defined according to three parameters; extension, severity and subjective perception.

Basically, the mentioned tests give a severity classification according to the score obtained. It can be classified as mild, moderate or severe. Taking SCORAD as reference, the scale goes from 0 to 104 points, and ranks as "mild" when patient is below 15 points, 16 to 40 "moderate", and over 40 "severe".[51] Nevertheless, the clinical history should be considered to assess the severity of symptoms, like the presence of comorbidities, the response to drug treatment and the duration of previous symptoms. All these parameters can help to predict the evolution and prognosis of the patient.[50] Recently some European guidelines[53] proposed to classify patients with transient symptoms as "mild", recurring as "moderate" and persistent as "serious". This is an interesting proposal because new variables are included. However, it must be validated, and it carries the risk of many patients rated only by the persistence of symptoms as serious, even if they are not (eg, patients with SCORAD <15).

Phenotypes

Phenotypes according to sensitization. Classical dermatitis classification divides patients in intrinsic or extrinsic according to the presence or absence of sensitization to an allergen.[54] Basically this classification divides patients in extrinsic dermatitis when they have high levels of total IgE (generally accepted > 200 kU/L), or a demonstrated sensitization to aeroallergens or food allergens. The term intrinsic dermatitis is applied when patients do not meet any of these criteria. This division was made thinking that there were two separated immunological processes,[55] but currently there is another hypothesis proposing that both immunological mechanisms are part of the same process in different periods of time, where the intrinsic dermatitis is the initial phase and extrinsic dermatitis the final phase, but this is under research.[56] These hypotheses are not mutually exclusive and each one may represent a different group of patients.

The population characteristics in Latin America, especially in the tropical area, make it necessary to consider some issues when using this classification. We now know that up to 20% to 40% of the general population without allergic symptoms may have sensitization without clinical relevance.[57] A big part of the non-allergic population in Latin American cities seem to have total IgE levels above 200 kU/L,[58] so this cutoff would not serve as a criterion for classifying dermatitis as intrinsic or extrinsic. This higher concentration of total IgE in the tropical population seems to be due to the high frequency of helminthes infections. There is the additional complication that some of these parasites such as

Ascaris lumbricoides, have cross-reactivity with some mite's proteins,[58,59] which makes it difficult to interpret the clinical relevance of sensitization.

Phenotypes according to immunological changes. Parallel to the better understanding of the pathophysiology of AD, a more accurate classification has been developed to allow, through the use of multiple biomarkers, a greater certainty in the prediction of the evolution of dermatitis, and also to define a more effective treatment for each patient. Three processes that may occur in parallel or sequentially have been described in patients with dermatitis. In the first process, is observed a predominantly Th1 response characterized by the expression of cytokines such as IL-1, IL-6, TNF-beta, and dendritic cells with few exilon receptors in the membrane. This process predominates in those patients classified with intrinsic dermatitis and in patients with extrinsic dermatitis during inter-critical periods; in this process, defects in the epithelial barrier are generally less severe, and in a significant percentage of patients, symptoms disappear with time. In the second process, there is a predominance of Th2 response characterized by both airborne and food allergen sensitization and can be started in a spontaneous way or in patients who previously had a predominantly Th1 response.[60] This process is often associated with asthma, has lower remission rate and greater severity. It is often associated with defects in filaggrin gene, which may be suspected from some clinical data such as palmar hiperlineality and eczema herpeticum.[23] The third process is the presence of an autoimmune response mediated by IgE. It is suggested that this may be due to the homology between human proteins and allergens from other species, and represent the most serious phase in a patient with dermatitis as a result of the persistent exposure to intrinsic allergens.[61-63]

These three processes represent different "endo-phenotypes" of the dermatitis and their identification would predict the likelihood of remission and the treatment required (whether or not avoidance of allergenic sources, treatment with topical or systemic immunomodulators, etc.).[64] As mentioned in the previous section, although these processes may occur separately, can also be different stages of a single process where Th1 (process 1) is the first step response, the Th2 response (process 2) the second stage and sensitization to auto-allergens (process 3) the final stage.[60] Although the identification of endo-phenotypes is promising in the diagnosis and treatment of atopic dermatitis, the procedures necessary to implement this classification, specially the final stage, are not widely available.

Classification according to age of presentation. 80% of the cases usually begin before age 2.[65,66] Of the 192 children included in a multicenter birth cohort from Germany (Cohort MAS), 43.2% had a complete remission between 2 and 7 years of age, 18.7% persisted with symptoms and 38% had an intermittent pattern with occasional relapses. The persistence of symptoms seemed to be determined by the severity and the presence of lower respiratory symptoms. 72.2% of children with persistent symptoms had an early onset (before the first year of life) and greater severity, while the majority of children with intermittent symptoms and minor scratching, had a later onset (Over first year) (OR = 5.86, 95% CI = 3.04 - 11.29).[65] As mentioned in the "Risk Factors" section, in Latin American cities seems to predominate an even later onset (> 3 years)[42] similar to that found in some European and Asiatic countries and it is not correlated with the severity of symptoms.[6,36]

The onset of disease in adulthood (> 14 years) may occur in up to 20% of patients and these cases have been little studied. A study conducted in Germany by Garmhausen et al.[67] found that in 725 adolescent and adult patients with dermatitis, 45% have had onset before 6 years,

10% between 6 and 14, 13% between 14 and 20 and 18% after 20 years. Sensitization and total IgE levels were higher in the groups with earlier onset, but the persistence of symptoms was higher in those who had onset after age 20. This is in contrast to the Cohort MAS, which found that over 80% of patients with dermatitis initiated symptoms before age 2. Since both studies were performed with German population, we can assume that environmental and anthropological changes rather than genetic inheritance could influence the different courses of dermatitis.[65] One study evaluating the treatment of atopic dermatitis indicated that success in controlling eczema is directly related to early intervention and a multidisciplinary treatment. This is important considering as it may determine, at least in a subgroup of patients, the type of development that will have the disease in its future.[68]

Laboratory test

IgE total

Patients with dermatitis (and any other allergy) usually have high levels of total IgE. The clinical relevance of total IgE in the diagnosis and monitoring of patients with atopic dermatitis has been studied broadly. A study in Japan found that between 16 biomarkers, only total IgE levels at 6 months of life in patients with dermatitis was an important predictor of persistent disease at 14 months of life.[69,70] Similarly, in Spain, total IgE levels were higher among patients with dermatitis during an exacerbation.[71,72] Other researchers found that 20 children with dermatitis and elevated IgE levels higher than 10,000 kU/L compared with 56 children with dermatitis and IgE levels between 400 to 1,000 kU/L had a higher rate of sensitization and greater severity.[73] The clinical response of systemic treatments such as the use of azathioprine,[74] gammaglobulins,[75] immunotherapy[76,77] and topical treatment with calcineurin inhibitors and steroids[78] appears to be associated with a reduction in total IgE, which would recommend the use of total IgE as a specific marker of control. However, several factors preclude routinely recommendation of the use of Total IgE in patients with atopic dermatitis; not all studies show a clear correlation between total IgE levels and clinical improvement and in some patients high total IgE levels may persist elevated for a long time, even with a significant improvement in clinical symptoms.[75,79,80] Another factor to consider is that parasites infection can elevate levels of total IgE, specially in Latin America population, where parasites infections are an endemic problem, making it difficult to establish cutoff to predict the response to treatment.

Indication. Diagnostic extrinsic or intrinsic dermatitis. Evaluation and monitoring of patients with atopic dermatitis.

Committee recommendation. Weak. May be used in patients younger than 6 months with severe dermatitis and in patients over 5 years old with persistent severe symptoms.

Particular considerations in Latin America. It is necessary to know the "normal" values of total IgE in different regions of Latin America to recommend performing this test routinely.

Allergen sensitization

Sensitization can be assessed by measurements of serum specific IgE or skin prick test. Sensitization to various sources of allergens in early life (especially food) may be transient, but atopic dermatitis patients are usually sensitized to a larger number of sources than asthmatics or rhinitis patients.[81] Some cohorts in Europe indicate that sensitization to food in children with dermatitis, occurs in the first years of life (<2 years) and is then replaced by sensitization to aeroallergens. This behavior does not seem to be shared by most of the tropical populations, where sensitization

to mites usually starts even before the first year of life among patients with allergic symptoms.[42,82]

In Europe, levels of specific IgE (especially mites and cat dander) appear to be associated with the severity of symptoms.[83] High serum concentration or skin prick test have been associated with an increased risk of reactions to foods, especially in patients with severe dermatitis.[84-86] In the city of Medellin (Colombia), a correlation was observed between a pattern of sensitization to allergen sources (mites, dog dander, pigeon droppings, mold and cockroach) and the parallel development of atopic dermatitis and asthma, which indicates that the pattern of sensitization could predict the severity of disease and the development of the "atopic march".[87] However, care must be taken in the interpretation of the results because patients with dermatitis may have a high frequency of sensitizations without clinical relevance, and performing unnecessary avoidance measures can lead to poor patient adherence to therapy and important impairment to their quality of life. In a recent review of the epidemiology of food allergy in Latin America, it was observed that the behavior of food allergy is different to that reported in other countries; sensitization to milk and egg was important but less frequent than other sources as corn, tomato and pork.[88]

The sensitization to microbial proteins was observed in 50% to 80% of patients with dermatitis and has been correlated with AD severity.[89-91] There has also been observed a greater sensitization to *Malassezia furfur* (previously called *Pityrosporum ovale*), although this has not been clearly correlated with the severity of symptoms.[92,93] The usefulness of measuring these extracts in patients with atopic dermatitis is still unclear.

The response against some auto-allergens (Hom s called because they are derived from the *Homo sapiens*) appears to be specific for patients with severe atopic dermatitis,[61-63,94] which would allow predicting patient prognosis. However, extracts required for these tests are not commercially available.

Indication. Diagnosis and monitoring of patients with atopic dermatitis. Identification of environmental sources exacerbating symptoms.

Committee recommendation. *Aeroallergens*: Strong. All patients with dermatitis. *Food allergens*: Strong. Recommended only in patients with clinical suspicion or serious and/or persistent presentations. The test battery should be consistent with the geographical area where the patient lives.

Particular considerations in Latin America. In Latin America there are many studies that provide insight into the most relevant aeroallergens, but there are few studies evaluating food allergens from the region.[88,95]

Patch test with food and/or aeroallergens

The underlying mechanism to be detected by the path test is the presence of T lymphocytes that mediate late reactions in patients after exposure to different sources.

The food patch test usually includes soy, wheat, egg and milk, but many other foods have been tested. Several articles support the usefulness of this test, especially in patients with atopic dermatitis.[96,97] Due to the wide range in the predictive values (40% to 80%) and the lack of standardization of the technique, the test has been criticized and rejected by several groups.[98] However, it is used in several centers because of its easy realization and potential utility detecting allergic processes mediated by T lymphocyte. In addition, some studies suggest that this test can reduce the requirement for provocation test and

avoid unnecessary restriction diets when is done with skin prick test.[99,100] The patch with aeroallergens especially mites has also been studied;[101] however, there are very few studies that validate its routinely use and also lacks a standardized universally accepted method.

Indication. Evaluation and monitoring of patients with atopic dermatitis and suspected delayed reactions with food allergens or aeroallergens.

Recommendation of the Committee. *Recommendation for food test*: Moderate. Patients with clinical suspicion of a particular food with negative IgE response or late-onset symptoms. *Recommendation for aeroallergens path test*: Weak. Few controlled studies. The battery must be consistent with the geographic area where the patient lives, yet few controlled studies are available and these usually include only soy, wheat, milk and egg.

Particular considerations in Latin America. In Latin America there are few studies evaluating the usefulness of the patch test, and results are in favor of its use;[102] however, it is necessary to standardize the technique and taste local products that could be cause sensitization.

Patch with standard battery and other types of patch

Contact dermatitis occurs frequently in patients with atopic dermatitis (15%-30%).[103,104] The inflammatory process in the skin, which facilitates the uptake of environmental antigens, can explain this. Patch test with standard battery is extremely useful in the identification of contact antigens.[105] However, in patients with dermatitis there is a high risk of false positives, so its use in patients should be limited to cases with a strong suspicion of exacerbation for a contact, or in those patients with persistent refractory to treatment presentations.

The use of photo-patch for drugs and path for any other battery (cosmetics, shoes, etc.), should also be performed when there is a strong clinical suspicion, and it should be remembered that the appropriate concentration of many cosmetics and medicines to patch test are not standardized. When there is not available a reference concentration, it is recommended to perform the test in ten healthy subjects as a control group, that reduces the risk of false positives by irritation, but does not reduce the risk of false negatives.

Indication. Patients with strong suspicion of contact dermatitis. Patients with persistent and severe AD, refractory to medical therapy.

Committee recommendation. *Standard battery*: Strong. *Other types of patch*: Moderate. Routine use is not recommended in patients with atopic dermatitis.

Particular considerations in Latin America. Studies in Latin America show the availability and the high value of these tests as diagnostic support.[106-108]

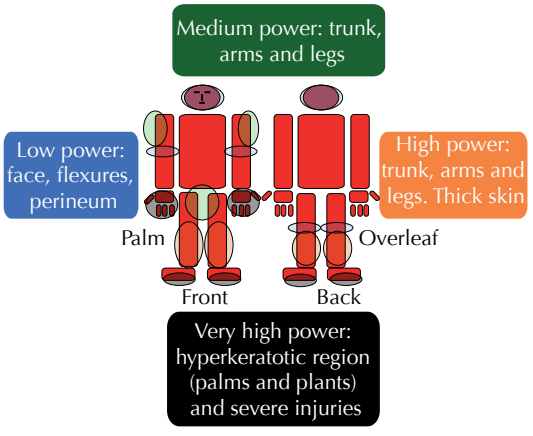

Figure 2. Topical steroids. Power of the steroid and application site.

Provocation and food elimination diet

The food challenge is the gold standard for identifying whether a suspected food is the cause of the patient's symptoms, but due to the risks of anaphylaxis and other severe symptoms, provocation should only be done when there are doubts in the diagnostic that cannot be clarified with skin tests and laboratory studies. Food symptoms can start immediately (pruritus, erythema) or later (worsening of eczema, new plates). In atopic dermatitis patients, is required long observation for days, even weeks, intercalated with food administrations to evaluate clinical changes.[109,110] Because of these difficulties, food restriction for 4 to 6 weeks with the suspect food (and all products containing it), may be preferable in certain situations. If doubt persists then the provocation is necessary.

Indication. Patients with suspected food allergy that has not been cleared with skin or serum tests.

Committee recommendation. Strong. We recommend initially performing the diet restriction, and if the relationship with food is not clarified it should be performed a controlled provocation.

Particular considerations in Latin America. As in the rest of the world, there are few studies in Latin America using provocation tests in the evaluation of food allergy in patients with dermatitis.[111] It is necessary to establish protocols with native foods.

Complementary studies

Laboratory tests as CBC, electrolytes, measurement of cortisol, liver function, kidney function, etc., are not indicated as routine exams. They could be indicated as part of the follow up when the patient requires the use of immunosuppressants such as cyclosporine, prolonged oral steroids, etc. Skin biopsy could be indicated for differential diagnosis.

ACTIVE MANAGEMENT

First line management

Skin care and hydration

Dry skin (xerosis) is one of the main symptoms of dermatitis and a key point in its pathophysiology. Xerosis may occur as a result of defects in filaggrin or lack of lipids and other particles in the stratum corneum leading to a lack of continuity of the barrier.[112] Due to the continuous skin peeling in these patients, the skin should be thoroughly cleaned during bathing, removing all debris that could stimulate bacterial growth. Drying seems to be even more effective than antiseptics to remove debris and prevent superinfection. Because long baths with very hot or very cold water may promote xerosis and make mechanical irritation, it is recommended short baths (<5 min) with slightly cold water. In patients with a history of skin infection, or in patients with risk of infection, is recommended to add one or two drops of hypochlorite per liter of water during bath to prevent bacterial growth.[113] The use of oils or bath salts in the final two minutes of the bathroom also favors greater skin cleansing and improved skin hydration. However, using soaps must be avoided, or if necessary, neutral products can be used in areas that require it (armpits, pubic areas, etc.). Moisturizing lipstick is also recommended for patients with cheilitis. The nails of patients with dermatitis should be cut frequently to avoid scratching during sleep, and baggy clothing is recommended, preferably make of cotton to avoid heat and irritation.[114] For what we know many of these products and measures appear to be useful, but there are few controlled studies demonstrating their effectiveness. Since in most health systems these products are not covered and are funded directly by patients, the cost/benefit relation should be considered.

Moisturizers appears to reduce the risk of bacterial infections,[115] severity of exacerbations,[116] steroid requirement[117,118] and seem to prevent relapse in patients.[119,120] Therefore, the use of moisturizers is considered as one of the pillars of the management of atopic dermatitis. It is recommended that the application of the moisturizing be performed after a short bathroom at least twice a day.[121] The type of moisturizer to use (with urea, coal tar petrolatum, ceramides, glycerin, olive-based, etc.) and the consistency (cream, ointment, gel, etc.) depends on the severity, the extension and patient's tolerance.[122]

To ensure good adherence, the above factors and the cost of the recommended products must be taken into account. It is necessary to explain to the patients how to use the creams given practical advices as the rule of the fingers (the amount of cream that covers a thumb must reach to cover the palm of hand). Some moisturizers such as vaseline are very economical and excellent in their function, but have the disadvantage of not being constantly used by patients for their oily consistency and a sense of heat and sweat retention. Moisturizers with urea are excellent

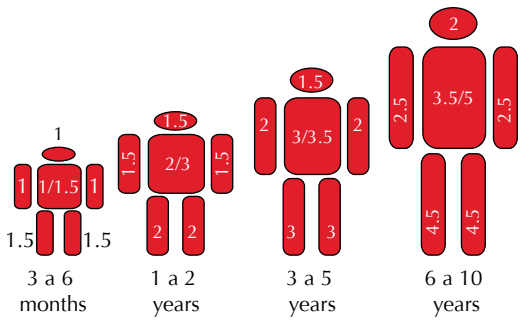

Figure 3. Finger tips units and application surface. A practical way to determine the amount of application is by the rule of the fingers: the tip of the index finger of an adult is used as a unit. The required amount of cream to cover a finger should reach for a palm of the hand. The amount to be applied will vary according to the age of the patient and the affected area. Chest/Back.

to accelerate skin renewal, however they tend to be less tolerated than other products so it is recommended to use them on skin with lichenification but without open wounds.[123] These products usually come from natural sources and some contain peanut protein, oats, olive, etc., therefore there is a small risk of sensitization and constant monitoring is needed.[124]

Indication. All patients with dermatitis. The frequency and intensity of use depend on the severity.

Recommendation of the Committee. Strong. Products that facilitate better patient adherence should be chosen.

Particular considerations in Latin America. Despite the growing evidence supporting the use of moisturizers as a pillar in the treatment of dermatitis, in most Latin American countries (and mostly in the rest of the world) health systems do not cover the use of emollients, so, at the time of the recommendation, factors such as cost/benefit must be considered to ensure a good response and good adherence.

Topical steroids

For anti-inflammatory treatment, topical steroids remain the cornerstone in the management of dermatitis.[119,125] They also appear to reduce the risk of infection by *S. aureus*.[126,127] Since patients with dermatitis may require prolonged use of steroid, justifiable concerns about the high risk of local and systemic adverse effects arise. However, when patient know how to use its appropriate scheme, these effects can be significantly reduced, so concepts as frequency and power should be explained. Several "soft" steroids of different power are available, which have a lower frequency of systemic side effects since they have an esterified molecule, which allows to be retained to a greater extent into the

skin, and are easily degraded when they enter to the circulation.[128-130] Despite the widespread and undeniable usefulness of steroids in dermatitis, there are few controlled studies supporting their uses or how to use them. Different schemes have been proposed in the use of steroids and some common points are present:

Steroids with high potency should be used only in patients with moderate to severe atopic dermatitis, and should be avoided in the facial, folds and perennial regions, and they must be used with caution in children under two years. They could be considered in those three areas previously described in exceptional cases and for periods not exceeding 7 days. In all patients they should be used for the minimum possible time and switching to medium or low power steroids according to the control of the patient. The continuous use of steroids for prolonged periods in wide body extensions (even mild steroids) can have similar risk of adverse effects than oral or intravenous steroids. The use of intermittent treatment appears to reduce this risk even with high potency steroids.[131]

Steroid use with moisturizer seems to improve the power of the steroid and increase the time of its effect on the skin, so it is recommended their joint application in mixtures or separately, according to the severity of the symptoms. Most oily moisturizers may promote absorption of steroids for its occlusive effect. Proactive management consisting of intermittent application of a low power steroid or calcineurin inhibitors, appears to significantly reduce the risk of relapse in patients under control.[119]

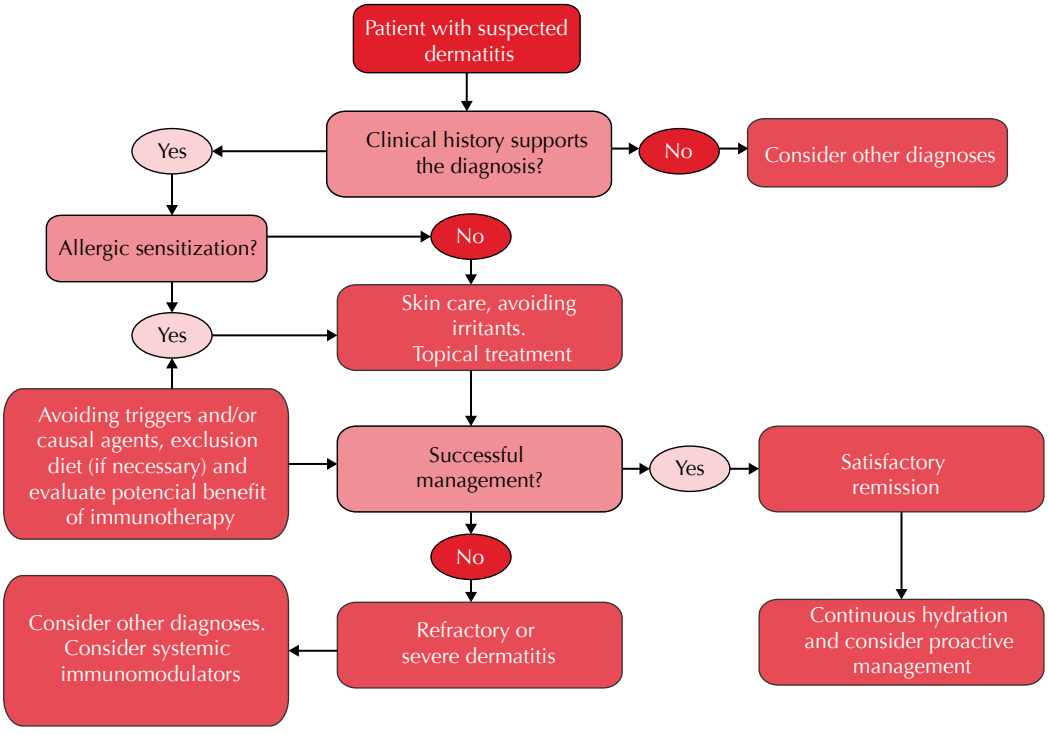

Figure 4. Management algorithm.

The application of steroids more than once a day seems to report no advantage but increases the risk of adverse effects, especially in the sensitive areas of the face or skin folds.

In acute injuries, it is advisable to mix the steroid with an emollient to prevent irritation in the area ant to increase absorption.

The application of occlusive steroid systems should be performed only by the indication of specialists (allergists or dermatologists).[130]

Indication. All patients with atopic dermatitis. The power of steroid and frequency of use will depend on the course and severity of patients.

Recommendation of the Committee. Strong. However, more controlled studies do not select the best scheme for each patient.

Particular considerations in Latin America. Latin America has a wide variety of steroids, allowing to calibrate the potency according to the needs of the patient. It must be taken into account the characteristics of the tropics and subtropics regions when choosing the consistency (cream, ointment, etc.) to improve patient adherence.

Calcineurin inhibitors

There are two topical calcineurin inhibitors: tacrolimus and pimecrolimus. Both have proven efficacy in dermatitis[132-135] in active and proactive treatment.[136] In practice, they can be used for the same indications as a steroid of medium (tacrolimus 1%) or low power (tacrolimus 0.03%, pimecrolimus 1%),[137,138] with the advantage that if continuous treatment is required, it will have a lower risk of adverse effects and it will not cause skin atrophy. However, it is necessary to avoid open injuries because they often produce burning feeling.[139] Other less common side effects include eczema herpeticum or molluscum.[140-142]

Although there is no evidence to show a causal relationship between cancer and the use of topical calcineurin inhibitors, it is recommended to be aware of the possible association during follow-up of patients.[138]

Indication. All patients with atopic dermatitis for active and proactive management.

Recommendation of the Committee. Strong in the above indications.

Particular considerations in Latin America. Currently in most Latin American countries both tacrolimus and pimecrolimus are available.

Allergen-specific immunotherapy

In the last two decades several controlled studies have been conducted showing that a significant percentage of patients with atopic (or extrinsic) dermatitis can benefit from this therapy, although impact varies according to the severity of patients.[143-147] A study conducted in the city of Medellin (Colombia) showed that patients with moderate dermatitis according to the SCORAD, had a greater and more significant reduction in symptoms compared to placebo, as well as a significant increase in IgG4.[80] These results are similar to those observed in other studies (147), but there is a need of additional studies to characterize better the patients who can benefit from this therapy. Several reports have shown that some patients may experience exacerbation of cutaneous symptoms and even systemic symptoms with immunotherapy, however, when the administration is controlled especially with modified extracts, the risk of systemic reactions is greatly reduced as observed in a retrospective study, where 114 patients with dermatitis which were applied over 1000 injections, and none had a systemic reaction nor abandoned therapy for the exacerbation of symptoms during treatment.

Indication. Patients with persistent moderate or severe atopic dermatitis who have a clear relationship of exacerbation with aeroallergens.

Recommendation of the Committee. Moderate. There are needed further studies to characterize which patients benefit most from this therapy.

Particular considerations in Latin America. There are some studies in Latin America that support the efficacy and safety of using the specific allergen immunotherapy with *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* in patients with dermatitis, but studies using other common allergen sources in the region as *Blomia tropicalis*, *Dermatophagoides siboney* and some pollen grains are needed.

Environmental and dietary control

Since the skin of patients with dermatitis is very sensitive, many agents can act as irritants increasing the inflammatory process and therefore should be avoided. Patients must learn to recognize irritant substances such as soap, detergents, some creams, polluted air and other specific factors present in their environment.[148,149] How strict must be patient with these measures will depend on its severity. If possible, patients should also perform a control of temperature and humidity of the room where they live.

Allergenic sources which patient is sensitized should be avoided. "Prophylactic" restrictions (removal of pets, restricted diets, etc.) when there is not a clinical relevance are not recommended. Recommendations should be very careful, particularly with diet, because in patients with dermatitis the number of irrelevant sensitizations can be high, so it is necessary to test only those foods with clinical suspicion to avoid confusion and unnecessary restrictions that can lead to nutritional problems in the patient.[150] Some steps to reduce the amount of allergens in the home as mop, cleaning with damp cloth, or removing pets (only when patient is sensitized) have been proposed, but few studies support that these restrictions lead to a significant improvement in the patient due to indirect exposure.[151-153] Unless there is a clear clinical relationship and sensitization is demonstrated, other factors such as emotional attachment should be taken into account before recommending the removal of pets, and it is necessary to consider that the amount of allergens from pets only starts to decrease significantly 3-4 months after removal.

Indication. All patients with dermatitis need to identify and avoid possible triggers of their illness. Allergy food studies should be performed in patients with clinical suspicion or persistent presentations.

Recommendation of the committee. Strong to the above recommendations.

Particular considerations in Latin America. It should be evaluated the environmental conditions of each patient and dietary customs, which are different in Latin America countries.[95,154]

Second line management

Antihistamines

Antihistamines have been used for many years in patients with dermatitis to reduce itching; however, the majority of controlled studies evaluating their effect show little or no effect in reducing pruritus,[155-157] perhaps because the itching in dermatitis have several pathways including the increased production of IL-33.[33] The preference of many physicians to use first-generation antihistamines for their sedative effect, must be balanced by the risk of side effects that chronic use of these drugs may have (low concentration, drowsiness, etc.).[158] Among the second generation, controlled studies with loratadine,

fexofenadine and cetirizine show that these drugs have small effect in the control of pruritus.[159-161] A recent study shows that antihistamines might promote a faster skin repair;[162] however, more studies are needed to assess the true impact of these medications as repairers of the skin barrier. Since patients with dermatitis often have other comorbidities, such as rhinitis, it is frequent the use of antihistamines.

Indication. According to the comorbidities of each patient.

Recommendation of the Committee. Weak. There is needed more studies evaluating the advantages and disadvantages of potential sedative and restorative effect in skin.

Particular considerations in Latin America. Due to the high frequency of comorbidities in patients with dermatitis in Latin America, the use of antihistamines is common, however, it should not be expected to control the itchy with this treatment alone.

Systemic steroids

It is clear that systemic steroids are useful in patients with severe disease, especially during exacerbations.[163,164] However, due to the high risk of adverse effects (cataracts, osteoporosis, height, etc.) they are not recommended for prolonged use. Oral stPPeroids have been associated with higher relapse rate after suspension compared with other immunosuppressants such as cyclosporine.[164] To avoid these adverse effects, it is recommended to adjust the dose according to patient weight and to reduce the dose. To achieve complete suspension reduce the doses until fully suspension once the patient gets control.[165] A used scheme is the administration of the full dose for 5-7 days, then half dose for another 5-7 days and last for three days and suspend interspersed. However there is no standard way to do this.

Indication. Patient with severe acute cases that do not respond to first-line management. It is not recommended chronically, even at low doses.

Recommendation of the committee. Strong for acute exacerbations.

Particular considerations in Latin America. The use of systemic steroids is quite popular in Latin America, unfortunately in many cases as chronic treatment. It is necessary to educate patient and physician to avoid overuse.

Sun exposure and phototherapy

An European study found that 74% of patients with mild to moderate dermatitis had a significant improvement over the summer with relapse in the other seasons.[166] Additionally, those who spent their summer days near the sea had greater improvement than those who passed it near the mountains. These results suggest that sun exposure (15 to 20 minutes a day from 7:00 to 8:00 am or 3:00 to 4:00 pm) has a beneficial effect. Since in the tropics high temperatures and humidity often accompany sun exposure, care should be taken when recommending controlled exposures because these conditions can exacerbate patient's pruritus. Phototherapy has the advantage that it is done in controlled environments and gives substantial improvement in 40 to 50% of patients with moderate or mild dermatitis.[167,168] Mechanisms leading to this effect are not clear yet, but it seems to be influenced by various pathways that produce an antimicrobial effect, inhibiting the activity of Langerhans cells and favoring the production of vitamin D.[169,170] Phototherapy can be performed with various wavelengths (UVB, broadband UVB, UVA1) being preferred short waves. Although its use has been studied primarily in adults, some data suggest that narrow band UVB can be used safely in children. Its indication is mainly in patients with refractory signs of lichenification, however,

some studies also suggest its use in acute exacerbations.[171,172] Exacerbations during phototherapy can be frequent (3%-20%) so the tolerance of each person must be carefully evaluated. Other side effects such as burns, hyperpigmentation fatigue, nausea and headaches can also occur with little frequency, while the more serious side effects, such as skin cancer, are less common, but patients should be warned.[173] There are few studies comparing the different types of phototherapy in dermatitis, so the advantages or disadvantages of one form over the other are not demonstrated for this disease.[174]

Indication. *Sun exposure*: All patients with annotated considerations to avoid itching. *Phototherapy*: Adult patient with recalcitrant symptoms that do not respond to first-line management.

Recommendation of the Committee. *Sun exposure*: Weak. There are no studies in the tropical and subtropical region. *Phototherapy*: Strong for chronic conditions in adults.

Particular considerations in Latin America. Although currently several centers in different countries of Latin America have phototherapy units, its use for dermatitis is rare.[175] This may be due to the difficulty in the mobilization and poor dissemination of this approach for dermatitis. Studies are needed in tropical and subtropical regions.

Cyclosporine A

Cyclosporine is a potent inhibitor of T lymphocytes immune response through binding to cyclophilin. Cyclosporine have a lot of studies evaluating its efficacy and safety.[176,177] A systematic review of the literature that included more than 10 trials in children and adults, concluded that this therapy is clinically effective but with a high relapse rate when suspended.[178] The clinical response is observed after two weeks reaching its greatest effect at 2 or 3 months. Despite its high efficacy, there is a significant risk of nephrotoxicity and hypertension, so the dose should be reduced to the minimum necessary and regular monitoring of blood test, blood pressure and renal function is required. Other common effects are nausea, abdominal pain and paresthesias.

Indication. Recalcitrant patient with severe symptoms that do not respond to first-line management.

Recommendation of the Committee. Strong to severe chronic conditions.

Particular considerations in Latin America. Currently there are no studies with cyclosporine and dermatitis in Latin America. However, it is available in most countries.

Third line management

Mycophenolate mofetil

Mycophenolate is an inhibitor of purine synthesis and it stops the division of several cell lines, including lymphocytes. Although there are numerous reports showing its positive effect in patients with dermatitis,[179] there are few controlled studies. Most reports show that in adults mycophenolate is generally well tolerated. Between its side effects are nausea, vomiting, retinitis and herpes. In an uncontrolled study with 14 children under 15 years of age, it showed a beneficial effect and a low rate of adverse effects, being mostly mild.[180] In a controlled study comparing the effect of mycophenolate and cyclosporine, it was observed that the rate of adverse reactions was lower for mycophenolate. However, at 6 weeks, patients with cyclosporine had fewer exacerbations and clinical improvement was superior than in the group with mycophenolate.[181]

Indication. Recalcitrant patients with severe symptoms that do not respond to the management of first and second line.

Recommendation of the Committee. Weak. Further studies are required.

Particular considerations in Latin America. While this drug is widely available in Latin America, there are currently no studies with mycophenolate mofetil and dermatitis in Latin America.

Azathioprine

Although the precise mechanism of action of azathioprine is not known, it has been used for many years in the management of dermatitis. Several controlled studies support its use, especially in severe cases with population over 6 years of age.[182-184] However, in these studies the rate of withdrawal is high due to the frequent incidence of adverse effects (nausea, vomiting, abdominal pain). It is necessary to monitorize patients with laboratory test. Four to eight weeks are usually enough time to evaluate the clinical response.

Indication.Recalcitrant patient with severe symptoms unresponsive to handling first and second line.

Recommendation of the Committee. Moderate. Although more studies are needed, it can be an alternative when cyclosporine is contraindicated.

Particular considerations in Latin America. Currently there are no studies with azathioprine and dermatitis in Latin America. However, it is available in most countries.

Methotrexate

Methotrexate has been widely used in various skin problems, especially in psoriasis. In the case of dermatitis, there are few controlled studies and therefore the appropriate dose and frequency of adverse effects is limited. In a comparative study, a similar effect was observed between methotrexate and azathioprine[185] and in two other studies doses of 10 to 25 mg per week showed a reduction in the severity of eczema.[186,187]

Indication. Adult patient with severe recalcitrant symptoms that do not respond to the management of first and second line.

Recommendation of the Committee. Weak. Further studies are required.

Particular considerations in Latin America. Currently there are no studies with Methotrexate and dermatitis in Latin America. However, it is available in most countries.

Fourth line management

Probiotics and prebiotics

Probiotics and prebiotics have been used on the prophylactic and active management of dermatitis. In a case-control study, Kalliomäki et al. found that early administration of *Lactobacillus rhamnosus* prevents the development of eczema in children under 4 years.[188,189] A review of Cochrane in 2007 based on 6 controlled studies published to that date, observed a reduction in eczema of children receiving probiotics prophylactically. But due to methodological biases, the authors concluded that there is not yet enough evidence to recommend adding probiotics in children at risk of dermatitis.[190] Another meta-analysis published in 2010 shows that the administration of *Lactobacillus* spp during pregnancy prevents development of eczema in children with 2 to 7 years.[191] These studies highlight that probiotics may have a positive effect in the prophylactic treatment, however there are still questions about the dosage and time of administration. Other important questions are what kind of strain is

the most appropriate for each population, since the effect of probiotics in part depends on the characteristics of the intestinal microflora of the population. Currently in Latin America, a study evaluating the intestinal flora observed that the presence of *Lactobacillus* spp, reduces the risk of wheeze in children under two years, and in this cohort the frequency of dermatitis before three years was zero. It is necessary to evaluate in the tropics if supplementation of probiotics or prebiotics produces the same effect.[192] Unlike prophylactic management, where the results are positive, most studies have shown little or no effect in the control of symptoms.[193,194] A meta-analysis published in 2013 that included 13 studies, concluded that more studies are needed before recommending the routine use of prebiotics in the prevention of allergies in children.[195]

Omalizumab

Although the current understanding of the pathophysiology of atopic dermatitis is incomplete, it is known that IgE play an essential role. Few studies have evaluated the effect of monoclonal anti-IgE in dermatitis but the results are promising.[196,197] Patients with atopic dermatitis have much higher levels of IgE than patients with asthma, so doubts arise about the required dose needed to achieve control of patients with dermatitis. The maximum recommended dose (450 mg) in patients with asthma by the laboratory is calculated for total IgE levels of 750 kU/L, but several reports suggest that even with this dosage, patients with severe dermatitis can achieve positive results even with total IgE levels greater than 1,000 kU/L.[198-200] Other studies have shown changes in immunological response but not clinical effect.[201,202]

IFN-γ

The gamma interferon (IFN-γ) is a cytokine that exerts its anti-inflammatory effect in dermatitis, inhibiting IgE synthesis and proliferation of T lymphocytes. IFN-γ has been shown to be effective in reducing eosinophil count of patients with dermatitis and to further improve control of symptoms in patients with severe disease.[203] A controlled study including 51 patients with severe recalcitrant dermatitis compared the clinical effect of low doses of IFN-γ (0.5×106 IU/m^2), high dose (1.5×106 IU/m^2), and placebo for 3 months of follow-up. Both groups treated with IFN-γ showed a significant reduction in the severity of symptoms compared to the placebo group, being faster in the higher-dose group but stable in both groups after two months. Potential adverse effects associated with IFN-γ are transient fever, myalgia, respiratory distress and elevation of transaminases and lipid profile.[203]

Other therapies

Some case reports have been published with several monoclonal like rituximab,[204-206] efalizumab,[207] aterizumab, alafacept, mepolizumab, and eternacept, but so far the results have been contradictory and in few patients, so they cannot be recommended in routinely use.[208] Intravenous immunoglobulin,[209] therapy with autologous serum[210] and some herbal products[211,212] are often used in some countries with satisfactory results, but the dosage, availability of extracts and frequency of use is not standardized and therefore it is difficult to recommend their use in Latin America.

Hospital management

The hospital management should be avoided because of the high risk of complications. However, when a patient with atopic dermatitis has a severe exacerbation with high risk of complication, hospitalization should be consider.[213,214] Some warning signs that suggest an imminent complication are:

Involvement of more than 50% of the skin surface with moist lesions or erythrodermia.

Sepsis or severe cutaneous infection, extensive or disseminated.

Involvement of other systems (respiratory, renal, etc.).

Limitation to perform their routine activities.

Failure to follow the established treatment.

The treating physician determines rapid deterioration.

Hospital management can ensure a continuous and adequate treatment for the patient and prevent further complications. However, due to the high risk of nosocomial infections and complications that it represent for the patient with dermatitis, other measures such as "hospital at home" may be more appropriate.

PREVENTION

Currently, there is no an intervention that has proven to be 100% effective in preventing the development of dermatitis or reduce its severity. However, the identification of modifiable risk factors permits to introduce indications that at least help to some of the population.

Primary prevention

Because dermatitis usually occurs in early childhood, primary prevention is intended, principally for newborn. Although some genetic factors appear to be protective as black heritage, they can hardly be used to create preventive policies. Most studies looking protective factors have been directed to the type of diet and avoidance of potential triggers as we discussed earlier. The preventive effect of vitamin D is extensively studied. Although several studies show a clear association between low levels of vitamin D and the development of atopy, asthma and dermatitis,[215] contrary to what would be expected, vitamin D supplement in diet as primary prevention in children younger than 3 years seems to be a risk factor for dermatitis.[216,217] The supply of vitamin D during pregnancy has been little studied and the results are also contradictory.[215,218] In a systematic review of the literature, it was observed that some foods could have a preventive effect on the development of dermatitis such as fruits, vegetables, unsaturated fatty acids, etc.[219] Supplementation with polyunsaturated fatty acids n-3 during pregnancy appears to reduce the risk of dermatitis in the newborn;[220] however, more controlled studies are required. Regarding pets, in a meta-analysis conducted in 2013, from 21 studies from birth cohorts, it was observed that the presence of dogs in the houses had a protective factor that reduced the risk of dermatitis by 25%. In the case of cats, it was not observed any risk or protective role.[221]

Secondary prevention

The goal of secondary prevention is to avoid common complications like exacerbations, bacterial superinfection with a worsening of severity. "Proactive management" has shown to be effective in preventing these complications as previously discussed (see "first line of management"). Probiotics have shown encouraging results in this regard and were treated in detail in the "fourth line management" section.

Several studies have shown that the use of topical antibiotics for a week every month seems to prevent new superinfections and it also decreases the severity of symptoms.[222] However, a meta-analysis conducted in 2010 did not observe significant statistically advantage with this therapy, and there is also a warning about the risk of microbial resistance to antibiotics.[194,223] Likewise, the use of oral antibiotics is not recommended unless the patient has an active infection. Despite disappointing results in primary prevention, vitamin D supplementation could be useful in a group of patients in secondary prevention. A

controlled study showed that supplementation of vitamin D during the winter appears to reduce the severity of injuries,[224] perhaps due to a possible antimicrobial effect on the skin.[225] The supply of other vitamins (E and K) and minerals have also been proposed as adjuvant therapy, but there is not enough information to recommend these alternatives.[211]

SPECIAL SITUATIONS

Pregnancy

Dermatitis is the most common skin disease during pregnancy (36-49%).[226] Histopathologically there is no difference between pregnant and non-pregnant patients.[227] Usually during the second half of gestation, 66% of patients present exacerbation of symptoms. Although the cause is unknown, this is attributed to the increase in Th2 polarization that normally occurs during pregnancy. However, among patients with non-atopic dermatitis there is also a worsening during pregnancy, therefore hormonal changes have been proposed as a possible cause.[227,228] Although dermatitis seems not to cause direct problems in pregnancy, bacterial infections could potentially promote premature births, abortions or fetal growth restriction.[229]

Treatment in pregnant patients is essentially the same as in the rest of patients. It is essential to try to get control using the least quantity of topical steroids to decrease the risk of systemic reactions.[226] It is also necessary to inform the patient the possibility of worsening during gestation. Although topical steroids are considered category C during pregnancy, the first-line treatment (hydration, steroids, etc.) is the same. Calcinuerin inhibitors, oral steroids, cyclosporine and azathioprine can be used only in case of extreme necessity, while the methotrexate, mycophenolate mofetil, psoralens and PUVA therapy should be completely avoided.[226] In the case of antihistamines, several first generation are considered category B (chlorpheniramine, cyproheptadine, diphenhydramine), this is because there are few studies with second-generation antihistamines, although loratadine appears to be a safe option.[230]

Breastfeeding

During lactation, it is necessary to note that the mother should restrict from their diet those foods to which the child is allergic, because some proteins can pass into breast milk and perpetuate symptoms in children.[231,232] This should be done only in cases of severe disease that fail to control with first-line therapy. Breastfeeding appears to have a beneficial effect inducing a tolerogenic response to different allergens from the diet, so it should not be suspended.[233] If the mother is receiving immunosuppressive drugs for dermatitis, she should take into account some considerations: Steroids can pass into breast milk but it seems that in small quantities. Cyclosporine should ideally be suspended during lactation, however it is not an absolute contraindication. No other immunosuppressive drugs are advised. Currently several second-generation antihistamines are approved for use after 6 months of age (loratadine, fexofenadine, cetirizine, ebastine, bilastine).

Adult dermatitis

Although a group of patients with dermatitis of childhood onset may reach adulthood without being able to con trol the disease, in 5 to 15% of patients the disease onset is after the age of 14.[67] The clinical action in these patients is essentially the same, however, the severity is usually higher and have a tendency to a greater number of non-allergic comorbidities.[234] In addition, the proportion of patients with allergic dermatitis is usually higher. In these patients, it may be necessary a first line biopsy and a patch test to rule out other processes.

Table 2. Immunosuppressive drugs

Medicament	Mechanism of action	Contraindications	Laboratory test	Efficacy	Recommendation of the committee
Cyclosporine: 2.5-4 mg/kg/day	Inhibits the proliferation of T lymphocytes	**Relative**: renal failure, hepatic disorders, pregnancy. **Absolute**: breastfeeding	**Basal**: BP, RF, HF, CBC **Track**: PA (fortnightly), RF, HF, CBC ideally graduate dose according to blood levels	50-70%	Strong
Phototherapy: Number of sessions depends on the patient's age and severity	No clearly defined	**Relative**: Pregnancy, children under 6 years	Clinical follow. CBC quarterly	40-70%	Strong
Azathioprine: 1 mg/kg/day, after 4 weeks two raised to 2 to 2.5mg/kg. Administer with meals	Inhibits purine synthesis and incorporation into DNA thioguanine	**Relative**: interact with allopurinol and warfarin. **Absolute**: pregnancy	**Basal**: BP, RF, HF, CBC pregnancy test, graduating Ideally dose according to levels of TPMT, evaluate lymphadenopathy. **Track**: (1, 2, 3 month then bimonthly): Sampling every 5-6 days after dose changes	30-80%	Moderate
Mycophenolate mofetil: 1 to 2g daily (max. 3g)	Inhibits the synthesis of guanosine nucleotides	**Relative**: infections, kidney failure, liver disease, pregnancy. **Absolute**: breastfeeding	**Basal**: BP, RF, HF, CBC pregnancy test. **Track (quarterly)**: trimestral paraclinical	60-80%	Weak
Methotrexate 5 to 25mg once a week	Folic acid analogue	**Relative**: deficit folic acid. **Absolute**: breastfeeding. Renal dysfunction, liver, DM, recurrent infections	**Basal**: HF, CBC, hepatitis A/B/C, FR, HIV (optional). **Track**: (2-4sem and then quarterly): CBC, platelets, RF	50-70%	Weak
Omalizumab	Blocks free IgE	**Relative**: parasites infection, dyslipidemia, abnormal ECG	**Basal**: CBC, lipid profile, ECG	30-50%	Weak
INF-gamma	Inhibits IgE production and T cell proliferation	**Relative**: recurrent infections	**Basal**: RF, HF, lipid profile, CBC, ECG. **Track (quarterly)**: CBC, platelets	40-62%	Weak

BP: blood pressure; RF: renal function; LF: liver function; CBC: blood count; ECG: electrocardiogram; G6PD: glucose-6-phosphate dehydrogenase; TPMT: thiopurine methyltransferase.

Interdisciplinary management

Patients with atopic dermatitis, especially those with severe presentations, require a multidisciplinary approach. Along with a disease specialist (allergist and/or dermatologist), there must be a close accompaniment with the pediatrician if the patient is a child.[235] Usually allergic comorbidities can be managed by the allergist, however, in places where there is no availability for this specialty or when a differential diagnosis is needed, the cooperation of the pulmonologist, the ophthalmologist or otolaryngologist may be required. All patients with dermatitis, must

have at least an annual assessment for ophthalmology and dentistry due to the high frequency of non-allergic comorbidities in the oral cavity and eyes.[235]

Patients with severe dermatitis, especially during adolescence, often have a higher frequency of psychological and psychiatric disorders like depression, anxiety, conduct disorders, autism, adaptive syndromes, or even suicide.[236] There seems to be a clear relationship between the severity of dermatitis and the severity of psychiatric disorders. Kemp et al.[12] observed that stress and psychiatric problems were presented with greater frequency and severity in patients with dermatitis than among patients with type 1 diabetes mellitus. Therefore, we recommend at least an annual assessment for psychology in all patients with severe symptoms.

COMPARISON WITH OTHER DERMATITIS GUIDELINES

Currently, there are available multiple guidelines and consensus for the management of dermatitis (Table 3).[165,237-241] All guides mentioned are focused on the management and were conducted by universities or scientific associations. Only ETFAD guideline and the guideline from the American Academy of Allergy Asthma and Immunology (AAAAI), use the GRADE system to define the level of evidence and to weigh the strength of the recommendation. The other guidelines were based on a review of the literature and on consensus opinion. These guidelines share several similarities in management of the disease, but since many of the treatments have no well-designed studies, guidelines also show some differences in the recommendations and in the strength of the recommendation. AAAAI guideline for example, recommends that the maximum duration of the shower should be ten minutes, while ETFAD guideline recommends five minutes. ETFAD guideline supports the use of phototherapy in a stronger way than in the AAAAI guideline, but the AAAAI guideline recommends its use in acute exacerbation, where ETFAD guideline does not recommend it. Regarding immunotherapy, AAAAI and ETFAD guidelines recommend it, while the Asian guidelines do not recommend it.

In the SLAAI guideline, we use the Delphi method for the development of the guidelines, and we used consensus and the GRADE system to assess the quality of evidence. The recom-

Table 3. Dermatitis guideline comparison

Feature	American Academy Allergy Asthma Immunology	European Task Force on Atopic Dermatitis	Asia and Japanese	Latin American Society of Allergy Asthma and Immunology
Year	2013	2012	2013/2009	2014
Methodology	GRADE	GRADE and DELPHI	Literature review and recommendation by consensus	GRADE and DELPHI
Institutions involved	AAAAI, ACAAI	EADV, ETFAD, EFA, ESPD, GA2LEN	Different Universities from Asia	SLAAI
Objective	Pathophysiology, diagnosis and treatment	Treatment	Treatment	Pathophysiology, diagnosis and treatment

AAAAI: American Academy Allergy Asthma Immunology; ACAAI: American College of Allergy Asthma and Immunology; EADV: European Academy of Dermatology and Venereology; ETFAD: European Task Force on Atopic Dermatitis; EFA: European Federation of Allergy; ESPD: European Society of Pediatric Dermatology; GA2LEN: Global Allergy and Asthma European Network; SLAAI: Latin American Society of Allergy Asthma and Immunology.

mendations are focused on the Latin American population considering sociodemographic characteristics, making this guide an important reference text when making decisions throughout Latin America. As mentioned in the introduction, it is necessary that all locations have their own management guidelines taking into account different geographical and cultural factors. However, as many other countries especially in Africa and Asia share the characteristics of the tropics and subtropics, this guideline can serve as a basis for the future development of similar documents considering particular factors present in those continents.

Authors' contributions

All authors contributed to literature review, writing the manuscript and editing the figures. All authors have read and approved the final manuscript.

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Abbreviations

Risk factors for the development of asthma and atopy in a tropical region (FRAAT), American Academy Allergy Asthma Immunology (AAAAI), American College of Allergy Asthma and Immunology (ACAAI), European Academy of Dermatology and Venereology (EADV), the European Task Force on Atopic Dermatitis (ETFAD), European Federation of Allergy (EFA), the European Society of Pediatric Dermatology (ESPD), and the Global Allergy and Asthma European Network (GA2LEN). Latin American Society of Allergy Asthma and Immunology (SLAAI).

Competing interests

The authors declare that they have no competing interests.

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