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Research Article

Pharmacological Management Of Atopic Dermatitis In Latin American Countries: An Evidence-Based Review And An Expert Consensus Statement Proposal

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ABSTRACT

Atopic dermatitis is a major chronic, pruritic, and inflammatory dermatological disease with a deep psychosocial and physical burden. Despite the numerous treatment options available, discrepancies exist between international guidelines. This work aims to make a review and expert recommendations by consensus statement of the pharmacological options available for atopic dermatitis in adults and children. The experts developed 15 consensus statements of the pharmacological management of atopic dermatitis. Additionally, treatment options were classified into topical and systemic options. However, a comprehensive management also includes adjuvant pharmacological options for infections and itching control. The doses, routes of administration, and precautions of all the recommended pharmacological options for atopic dermatitis in children and adults have been compiled in a single document.

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INTRODUCTION

Atopic dermatitis (AD) is the most frequent systemic, inflammatory, multifactorial, pruritic, and chronic skin disease worldwide. AD generally begins during the childhood (85%) and resolves at puberty in 50% of cases (1,2). A systematic review analyzed epidemiological studies and reported that each year up to 22.6% of children and 17.1% of adults were diagnosed with AD (3). The pathophysiology of AD is multifactorial, involving alterations of the immune system with increased production of Immunoglobulin E (IgE) and dysregulation of cytokines. Furthermore, AD presents dysfunction of the skin barrier in the lipid metabolism, structural epidermal proteins (filaggrin, claudin I and inhibitors protease), water loss, and microbiome alterations mediated by genetic predisposition, environmental exposure and psychological triggers (1,2).

The diagnosis of AD is only by clinical evaluation accounting for various signs and symptom such as skin lesion location and the personal and family history of atopic conditions (4). Basically, three items can provide the diagnosis of AD, pruritus, typical morphology and distribution of eczema, and chronic or chronically relapsing course regardless of symptoms severity (5). In addition, intense itching, sleep disturbance, deprived physical and mental performance, and psychological stress are hallmark features of AD impacting quality of life (6).

The treatment of AD is complex due to the disease heterogeneity in terms of clinical presentation and severity (2). The comprehensive management of AD includes its long-term control in terms of injury reduction and quality of life maintenance (1). These goals are achieved through educational strategies, prevention measures, pharmacological and non-pharmacological treatments that can be topical and/or systemic (7,8). Unfortunately, since basic care and nonpharmacological approaches against exacerbating factors are not sufficient to stabilize AD , pharmacotherapy will be needed to achieve disease control in many patients (9).

Recently, corticosteroids were the only FDA (Food and Drug Administration) approved systemic treatment for moderate-to-severe AD and patients were also treated with off-label immunosuppressive drugs with major adverse events (AEs) (10). Nowadays, new emergent immunosuppressant and biologic drugs with acceptable efficacy/safety are available for AD patients (10). Furthermore, they can also help treating complications such as infections and itch control (11). Despite the extant literature and guidelines on AD, major gaps remain concerning AD management (doses and safety) in all populations (6).

The recommendations compiled in this document were made through the review of the evidence and the consensus of experts. They reflect the experience, opinions, and guidelines of Latin-American's dermatology and allergology experts in AD pharmacological treatment.

Methods

Ten leading experts in dermatology, allergology and immunology from five Latin American countries (Costa Rica, Ecuador, Guatemala, Panama, and Dominican Republic) designed an online protocol template on the therapeutic management of AD according to the Appraisal of guidelines research & evaluation (AGREE II).

An extensive literature search of the last 8 years in English and Spanish was done in PubMed, Medline, and EBSCO. The keywords used for the research were "atopic dermatitis", "consensus", "guideline" and "drug treatment". In addition, updated international therapeutic guidelines were evaluated including reference drug agencies like FDA and EMA (European Medicines Agency).

Consensus was defined as approval by at least 70% of the panel. The AGREE II instrument was used to evaluate the process of the document development and the quality of reporting. It also provides criteria to appraise the quality of content and consists of 23 items

grouped in six domains (12). GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was used to evaluate the level of evidence of each recommendation.

Results

Pharmacological strategies for AD include topical and systemic therapies. The route of administration of selected drugs depends on patient characteristics and disease severity (2,8). However, AD comprehensive management also includes adjuvant therapy for controlling itching and infection complications (13). The main recommendations and consensus statement of the pharmacological management in AD outlined here are summarized in Table 1.

Table 1. Treatment recommendations and consensus statement for AD

Recommendations	Evidence level	Consensus statement
Topical pharmacological therapies		
Topical corticosteroids are recommended to reduce itching in AD. Topical corticosteroids should be used as a first line treatment along with appropriate use of moisturizing agents. Topical corticosteroids can be applied proactively as maintenance therapy. The FTU is recommended to assure an adequate amount of the drug on the different body areas.	1a	Topical corticosteroids can be applied in active areas of the disease for a short term (up to 14 days). The proactive modality as maintenance therapy with topical corticosteroids is recommended Topical corticosteroids can be applied with bandages or wet compresses to improve their efficacy, dilute their concentration, and reduce adverse events in active areas of the disease
Topical calcineurin inhibitors are recommended as first-line treatment along with appropriate use of moisturizing agents. Topical calcineurin inhibitors can be applied proactively as maintenance therapy. The FTU is recommended to assure an adequate amount of the drug on different body areas.	1b	Calcineurin inhibitors are recommended as first-line treatment in patients with mild-moderate AD. Before the application of calcineurin inhibitors is recommended to refrigerate them for 15 minutes to reduce the burning sensation (this burning sensation will decrease with use)
Topical antihistamines have shown low efficacy in control the itching in patients with AD	4	The use of topical antihistamines is not recommended for the management of pruritus in AD
The routine use of long-term topical antibiotics is not recommended due to the risk of resistance and sensitization Topical antifungals may be effective in some patients with AD who present with active infection located in the head and neck or with demonstrated sensitization by IgE to Malassezia spp	2a	Topical antibiotics are not recommended to prevent infections in AD
Crisaborole is recommended for the management of pruritus in patients with moderate to severe AD	2a	The group of experts considers crisaborole appropriate for itching control in AD, despite the lack of availability of the drug at the regional level
Systemic pharmacological therapies		

Systemic corticosteroids have an unfavorable risk-benefit ratio but may be a therapeutic option in the case of AD relapses. A starting dose of prednisolone of 0.5 mg/kg/day or equivalent is recommended, with a gradual decrease to reduce the risk of rebound	1b	Systemic corticosteroids are recommended in patients with moderate to severe AD without adequate response to topical therapies. Systemic corticosteroids should be used for a short time, no longer than one to two weeks Systemic corticosteroids are not recommended as first-line drugs but as bridging treatment to other systemic options
Cyclosporine A is recommended as the first therapeutic option for moderate to severe AD, in patients without adequate response to topical interventions	1a	The administration of cyclosporine A is recommended in patients with moderate to severe AD without adequate response to topical therapies or as an alternative to systemic corticosteroids
Azathioprine should be considered as a second-line immunosuppressant in adult patients without response or with adverse events to cyclosporine A	1b	AZA is recommended in patients with refractory AD without adequate response to cyclosporine A. The monitoring of coagulation function is important during the use of AZA
Methotrexate can be considered as a second-line treatment among immunosuppressants after cyclosporine A	3a	MTX is recommended in refractory AD without response to cyclosporine A. MTX should not be used during pregnancy. MTX can be used in the absence of other alternatives due to the low cost and good adherence in case of having the availability of health centers that helps with the administration of the drug (subcutaneous injection)
Mycophenolate mofetil has long-term safety and may be an alternative in adult patients without response or who have adverse events to cyclosporine A	1b	Mycophenolate mofetil can be used in adults and children with moderate to severe AD. However, it depends on availability and local access
Gamma interferon is poorly recommended in patients with moderate to severe AD due to the limited evidence	4	Gamma interferon is not recommended in patients with AD. Gamma globulin can be considered as an option in special cases of AD and according to availability (institutional - local - cost)
Dupilumab is recommended in adult and adolescent patients (> 12 years) with moderate to severe AD and childrens (> 6 years) with severe AD	1b	Dupilumab is recommended in patients with moderate to severe AD without response to topical interventions or with an inadequate response to cyclosporine A
Tofacitinib has insufficient evidence of efficacy and safety for AD	4	JAK inhibitors are not recommended for AD until there is sufficient evidence of their efficacy and safety
Adjuvant pharmacological therapies		

The use of antihistamines is recommended for the management of itching; however, their role is limited	1b	The experts reached a consensus based on their experience to recommend non-sedating antihistamines in most cases and sedatives exclusively in cases of sleep disturbances and cognitive impairment. In the case of pregnant patients, it is preferable to use non-sedating antihistamines
Topical and systemic antibiotics should only be used in case of infection with clinical evidence Long-term use of systemic or topical antibiotics should be avoided to reduce bacterial resistance and sensitization	1b	It is advisable to consult an infectiologist in the case of suspected infection in patients with AD Antibiotics should only be used in case of active infections. A culture of the nasal passages can be performed in case of recurrent infection, lack of clinical improvement, and suspected antibiotic resistance. Antibiotics are recommended based on local sensitivity patterns

Table 2. The potency of topical corticosteroids

Potency	**Generic name**
Class 1 (superpotent)	Clobetasol propionate 0.05% Halobetasol propionate 0.05% Diflorasone diacetate 0.05% Diflucortolone valerate 0.3%
Class 2 (potent)	Betamethasone dipropionate 0.05% Mometasone furoate 0.1% Halcinonide 0.1% Fluocinonide 0.05% Desoximetasone 0.25%, 0.05%
Class 3 (potent, upper/midstrength)	Amcinonide 0.1% Betamethasone dipropionate 0.05% Betamethasone valerate 0.1% Difluprednate 0.05% Desoximetasone 0.25%
Class 4 (midstrength)	Mometasone furoate 0.1% Methylprednisolone aceponate 0.1% Triamcinolone acetonide 0.1% Fluocinolone acetonide 0.025% Budesonide 0.025% Desoximetasone 0.05%
Class 5 (lower midstrength)	Fluticasone propionate 0.05% Triamcinolone acetonide 0.1% Hydrocortisone butyrate 0.1% Hydrocortisone valerate 0.2% Fluocinolone acetonide 0.025% Betamethasone valerate 0.05% Prednicarbate 0.25% Clobetasol butyrate 0.05% Prednisolone valeoroacetate 0.3%

Class 6 (mild strength)	Alclometasone dipropionate 0.05% Desonide 0.05%
Class 7 (least potent)	Hydrocortisone 2.5%, 1% Dexamethasone 0.1% Flumethasone pivalate 0.02% Flucortin butylester 0.75% Prednisolone acetate Prednisolone valeroacetate Hydrocortisone butyrate propionate

Source: Ann Dermatol (2015) [17]

Topical pharmacological management

An effective topical therapy should have sufficient resistance, dose, and correct application of drug (14). Topical options for AD include topical corticosteroids, calcineurin inhibitors, phosphodisterase-4 inhibitors, and Janus kinase inhibitors (2,8,14).

Topical corticosteroids

Topical corticosteroids are the first line treatment in AD due to their anti-inflammatory properties, especially during the acute phase of the disease (11,14). Corticosteroids are classified by their cutaneous vasoconstrictor potency in seven groups according to the American classification published by the World Health Organization (WHO) in 1997 (Table 2) (8,14). An acceptable tolerance has been demonstrated with the long-term use (up to 20 weeks) of topical corticosteroids applied twice a week. The "proactive" mode is also recommended, which consists of applying the product to the affected areas once or twice a day for 4 weeks and then twice a week on non-continuous days for 12 to 16 weeks to the same affected areas or "hot areas" (8,14). In active lesions, short-term use of potent corticosteroids is recommended for the shortest possible time, maximum 14 days (15). In the case of patients with extensive affected areas, the application of topical corticosteroids with wet compresses is indicated to dilute their concentration, maintain their anti-inflammatory effects and not aggravate their AEs (16). It is advisable to avoid the application of powerful corticosteroids in delicate skin areas (8). Fingertip Unit (FTU) is recommended to determine the quantity of topical product of corticosteroids. One FTU is equivalent to 0.5 g of topical corticosteroids, enough to cover the surface of one palms (17). Common AEs are thinning of the skin, development of telangiectasias, formation of pseudo scars, ecchymosis, stretch mark formation, “dirty” neck (punctate cutis Linearis colli), hypertrichosis, Cushing's syndrome, cataracts, and glaucoma (14). A “corticophobia” or phobia of AEs of corticosteroids in patients with AD has been described in the literature. However, published evidence recommends speaking to patients about adherence and risk of under-treatment (14).

Calcineurin inhibitors

The calcineurin inhibitors approved for AD are tacrolimus and pimecrolimus. These anti-inflammatory drugs are less potent than corticosteroids and have fewer AEs (8). A burning sensation is reported during the first days of application. These drugs do not induce epidermal atrophy and are indicated in sensitive areas of the skin (1,14). Of note, tacrolimus 0.1% ointment is more potent than pimecrolimus 1% cream and a biweekly application in “hot spots” is recommended to reduce relapses. Sun protection in patients using calcineurin inhibitors is mandatory (14). Age is important for appropriate drug administration. For example, pimecrolimus 1% (cream) and tacrolimus 0.03% (ointment) are recommended in patients older than 2 years, while tacrolimus ointment 0.1% should be used after 16 years of age (11). By contrast, pimecrolimus plus topical corticosteroid in active lesions or topical corticosteroids are recommended in children aged 3-12 months (18). A key recommendation is to appropriately examine the extent of inflammation to apply a sufficient degree of these agents (19).

Table 3. Systemic drugs for treatment of severe atopic dermatitis

	Cyclosporine	Methotrexate	Azathioprine	Mycophenolic acid	Corticosteroids	Dupilumab
Overall recommendation	++ acute flare Intervention	++ long-term maintenance	Can be used long term	++ little toxicity	Outdated‡	Long-term maintenance
Time to respond (weeks)§	2	8–12	8–12	8–12	1-2	4-6
Time to relapse (weeks)	<2	>12	>12	>12	<2	>8
Most important side-effects	Serum creatinine ↑ blood pressure ↑	Hematological liver enzymes ↑ gastrointestinal	Hematological liver enzymes ↑ gastrointestinal	Hematological skin infections gastrointestinal	Cushing's osteoporosis diabetes	Conjunctivitis
Starting dose adult	4–5 mg/kg/day‡	5–15 mg/week	50 mg/day‡	MMF 1–2 g/day (EC-MPA 1.44 g/day)	0.2–0.5 mg/kg/day	600 mg loading dose
Maintenance dose adult	2.5–3 mg/kg/day	Most often 15/week; can increase to max 25 mg/week	2–3 mg/kg/day†	MMF 2–3 g/day (EC-MPA 1.44 g/day)	Not for maintenance‡	300 mg/2 weeks
Starting dose children	5 mg/kg/day	10–15 mg/m2/week	25–50 mg/day	MMF 20–50 mg/kg/day	0.2–0.5 mg/kg/day	No data yet
Maintenance dose children	2.5–3 mg/kg/day	Increase 2.5–5 mg/ week, decrease 2.5 mg/ week to effective/lowest effective dose	2–3 mg/kg/day†	Increase daily total dose by 500 mg every2–4 weeks up to 30–50 mg/kg/day	Not for maintenance‡	No data yet
Pregnancy	Possible	Teratogenic, absolutely contraindicated	Conflicting data, possible with strict indication	Teratogenic, absolutely contraindicated	Possible	No data yet
Fathering	Possible	Little information, conflicting data, contraindicated	Little information, possible with strict indication	Conflicting data	Possible	No data yet

†TPMT heterozygote 1–1.5 mg/kg/day. ‡See full text. §Time to reach most of expected full response. EC-MPS, enteric-coated mycophenolic sodium; MMF, mycophenolate mofetil.
Source: European Academy of Dermatology and Venereology (2018) [14]

Topical antihistamines

Topical antihistamines evidenced little utility for pruritus but they generate AEs such as skin hypersensitivity and alteration of the skin microbiome which limit their risk/benefit use (8).

Topical antimicrobials

The skin of AD patients is prone to over-infection due to the imbalance between normal flora and pathogenic microorganisms (bacteria, viruses, and fungi). Furthermore, dry skin, itching, and inflammation predispose skin to be easily colonized and infected (8). The application of topical antibiotics as prevention of infection is not recommended due to the risk of resistance and bacterial sensitization. They must be exclusively used in active infections (14). In case of fungal infection by Malassezia located in the head and neck, topical antifungals such as ketoconazole and cyclopyroxolamine can be used (1,2) but lack evidence in large-scale studies (19).

Phosphodiesterase-4 inhibitors

Crisaborole is a topical phosphodiesterase-4 inhibitor that prevents the production of pro-inflammatory cytokines in AD lesions, reducing pruritus and clinical severity (11). This drug was approved by FDA for the management of patients > 2 years with mild-moderate AD (2).

Table 4. H1 antihistamines by degree of sedation and their doses with route of administration

Antihistamine	Dose, route of administration
High degree of sedation	
d-chlorpheniramine	5 mg, IV
Ketotifen	1 mg, PO
Hydroxyzine	30 mg, PO
Diphenhydramine	30 mg, PO
d-chlorpheniramine	2 mg, PO
Moderate degree of sedation	
Oxatomide	30 mg, PO
Astemizole	10 mg, PO
Cetirizine	20 mg, PO
Mequitazine	3 mg, PO
Azelastine	1 mg, PO
Low degree of sedation	
Bepotasin	10 mg, PO
Olopatadine	5 mg, PO
Cetirizine	10 mg, PO
Terfenadine	60 mg, PO
Loratadine	10 mg, PO
Ebastine	10 mg, PO
Levocetirizine	5 mg, PO
Epinastine	20 mg, PO
Bilastine	20 mg, PO
Fexofenadine	120mg, PO

Abbreviations: IV - intravenous, PO - orally
Modified from: Allergy Magazine Mexico – 2015 [37]

Systemic pharmacological management

Specific systemic treatments for AD unresponsive to topical treatment include systemic corticosteroids, cyclosporine A, azathioprine (AZA), mycophenolate mofetil, methotrexate (MTX), and gamma interferon (IFN-γ). The only biologic agent currently approved for adults, adolescents (>12 years) and children (6-11 years) with moderate to severe AD is dupilumab (IL 4 and IL13 inhibitor) (14). Indications, response time, relapse time, dose (initial, maintenance) and the impact on pregnancy and fathering of the specific drugs approved in AD are described below and summarized in Table 3 (14).

Systemic corticosteroids

The use of systemic corticosteroids significantly improves the symptoms of AD. However, their use should be limited due to their AEs and rebound phenomenon. Therefore, they are recommended in case of disease relapse and in case of non-response to topical therapy (11). Short-term treatment, up to 1 week, with oral corticosteroids is recommended for the management of relapses in exceptional cases of AD. Their use is limited to a maximum daily dose of 0.5 mg/kg and close monitoring by the doctor (2).

Cyclosporin A

Cyclosporin A, a calcineurin inhibitor that suppresses the transcription of numerous cytokines, is considered the most effective non-biological non-steroidal immunosuppressant in AD but since it is not approved in all countries its access varies (11,16). The safety and efficacy profile of cyclosporin A allowed to be recommended in patients over 16 years with failure of first-line therapy. Furthermore, it can be used in children older than 2 years up to a maximum of 1 year or intermittently with cycles of 3 to 6 months with the same adult doses (11). Short cycles with cyclosporin A are

generally recommended, although long-term use in low doses has been shown to be effective and safe in patients with AD (20). Reported serious AEs of cyclosporine A include nephrotoxicity, infection, hypertension, electrolyte problems, tremor, hypertrichosis, headache, gingival hyperplasia, and non-melanoma skin cancer and only nephrotoxicity was irreversible (11). Cyclosporin A therapy should be quickly switched to conventional topical treatment after the relief of symptoms (19). A systematic review concluded that serum levels of cyclosporine should be recommended in specific pediatric groups (children receiving multiple medications), in patients with liver or kidney failure, and in non-responders (21).

Azathioprine

Azathioprine (AZA) is an immunosuppressant used in moderate to severe AD although not approved for this indication by FDA and EMA. Several placebo-controlled clinical trials have shown its efficacy in improving the quality of life in AD patients (2,5). Evidence strongly recommends in AZA treatment to measure the levels of the TPMT (thiopurine methyltransferase) enzyme before starting the treatment (11). The most common AEs with AZA were gastrointestinal symptoms, leukopenia, elevated liver enzymes, bone marrow aplasia, increased risk of non-melanoma skin cancer, and lymphoma (1,2). Lastly, AZA had a D-category in pregnancy due to the teratogenic risk and its use should be avoided in these cases (22).

Methotrexate

Methotrexate (MTX) is an immunosuppressant indicated for the initial treatment in moderate to severe AD. It reaches clinical efficacy after 8 to 12 weeks of administration (1). In addition, the administration of folic acid is recommended 1-2 days after starting the treatment and it is important to remember its teratogenic effect (1,2). Therefore, the use of contraceptives is mandatory during the administration (1). One reference recommended MTX and AZA in adults with moderate to severe AD because of their efficacy/safety in long term administration (3).

Mycophenolate mofetil

Mycophenolate mofetil is a drug approved in Europe for the management of systemic lupus erythematosus and for the prevention of transplant rejection (2). The drug is also used in AD because of its immunosuppressive properties in AD patients with an inadequate response to cyclosporine A (11). Available evidence based on case reports and randomized clinical trials supported the use of mycophenolate mofetil in adult patients with AD despite limited information on optimal doses and appropriate treatment duration (14). The most common AEs included gastrointestinal symptoms (nausea, diarrhea), hematological symptoms (anemia, leukopenia, and thrombocytopenia) and genitourinary problems (urinary urgency and dysuria) (2,11).

Gamma interferon and intravenous immunoglobulin

Gamma interferon has a lack of published evidence to support the use in AD. However, the drug can be used in patients with severe AD lacking response to cyclosporine A (23). The most common AEs are intermittent headache, myalgia, and chills (23). On the other hand, high doses of intravenous immunoglobulins have reported an improvement of 61% in AD patients. Of importance, this drug had a better response in children than adults (90% vs 48%) and can be used as an adjuvant therapy versus monotherapy (59% vs 0%) (11).

Biological agents

Several biological agents for moderate to severe AD are currently under study, but only dupilumab has been approved by international regulatory agencies for the management in adult and adolescent populations.(1,2)

Dupilumab

Dupilumab is a monoclonal antibody that blocks the alpha chain of the IL4 and IL13 receptor (1). Dupilumab was approved by the FDA (2017) for the management of moderate to severe AD in adult patients. It has been shown to be effective for at least one year of treatment and its safety profile was appropriate (2,11). The main adverse event with dupilumab was conjunctivitis present in 16% of patients (24).

In adolescents weighing less than 60 kg the recommended dose of dupilumab was 400 mg followed by a maintenance dose of 200 mg every 2 weeks, while in adolescents weighing 60 kg or more the starting dose was 600 mg followed by 300 mg every 2 weeks (24). In May 2020, the FDA approved the use of dupilumab in children aged 6-11 years with moderate to severe AD. Dupilumab reported favorable results in reducing pruritus, an improvement of at least 75% of the disease according to the Eczema Area and Severity Index (EASI), and a safety profile consistent with that reported in adolescents and adults versus corticosteroids alone. The doses approved were according to weight (300 mg every 4 weeks in children 15-30 kg and 200 mg every two weeks in children 30-60 kg of weight, both after an initial loading dose) (25).

Table 5. Antibiotics, antivirals and antifungals used in AD

Drug	Administration route	Adult doses	Pediatric doses	Pregnancy category	Precautions	Adverse events
Systemic antibiotics						
Penicillin G Potassium	IV	5 to 24 million units/day divided every 4 to 6 hours	150,000 to 300,000 units/kg/day divided every 4 to 6 hours	B	Allergic reactions in 0.7 to 10%. Clostridium difficile infection	Positive Coombs hemolytic anemia, hemorrhagic diathesis, hypercalcemia, interstitial nephritis, seizures, coma
Amoxicillin / clavulanic acid	PO	500 mg BID or 250 mg TID	20 to 25 mg/kg/day divided every 8 or 12 hours in patients under 40 kg. Children >40 kg follow adult doses	B	Anaphylactic shock due to allergic cross reaction in patients allergic to penicillin. Clostridium difficile infection	Hepatotoxicity, interstitial nephritis, hemolytic anemia, thrombo-cytopenic purpura, increased prothrombin time, anxiety, confusion, seizures, tooth discoloration
Doxycycline	PO	Initial dose: 100 mg BID on day 1 Maintenance dose: 100 mg/day QD	Children over 8 years. Weight ≤45 kg: Initial dose of 2.2 mg/kg divided into two doses on day 1. Maintenance dose 2.2 to 4.4 mg/kg/day QD. Weight >45 kg dose the same as adults	D	Tooth discoloration in children under 8 years of age. Clostridium difficile infection	Photosensitivity exfoliative dermatitis, hemolytic anemia, thrombo-cytopenia, neutropenia, eosinophilia, esophagitis, esophageal ulcers
Oxacillin	IV	250 to 500 mg every 4 to 6 hours	100 to 200 mg/kg/day divided every 4 to 6 hours	B	Anaphylactic shock in 0.015 to 0.04% of patients with allergy to penicillin. Clostridium difficile infection	Tubular kidney damage and interstitial nephritis, hepatotoxicity, neurotoxic reactions
Cephalexin	PO	250 mg every 6 hours	24 to 50 mg/kg every 6 hours	B	Anaphylactic shock due to allergic cross reaction in patients allergic to penicillin (10%). Clostridium difficile infection	Aplastic anemia, pancytopenia, renal toxicity, prothrombin time prolongation, seizures
Cefuroxime	PO	250 to 500 mg BID	Children under 12 years: 30 mg/kg/day divided into 2 doses (oral suspension) or 250 mg BID (tablets)	B	Anaphylactic shock due to allergic cross reaction in patients allergic to penicillin. Clostridium difficile infection	Eosinophilia, hemolytic anemia, pancytopenia, hepatotoxicity, seizures, encephalopathy, renal dysfunction, epidermal toxic necrolysis

Trimethoprim sulfamethoxazole	PO	160 mg/800 mg BID	Patients older than 2 months. 8 to 12 mg/kg/day divided into two doses	D	Risk of congenital malformations. Clostridium difficile infection	Thrombo-cytopenia, epidermal toxic necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, toxic nephrosis, aseptic meningitis, seizures, depression, rhabdomyolysis
Clindamycin	PO	150 to 300 mg every 6 hours	8 to 16 mg/kg/day divided into three to four doses	B	Clostridium difficile infection	Toxic epidermal necrolysis, exfoliative dermatitis, esophageal ulcer, polyarthritis
Gentamicin	IV or IM	3 to 5 mg/kg/day divided into 3 doses	Children <40 kg: 2 to 2.5 mg/kg TID. Children >40 kg dose the same as adults	D	Risk of congenital malformations, congenital deafness	Nephrotoxicity, ototoxicity, seizures, respiratory depression, pulmonary fibrosis
Erythromycin	PO	500 mg BID	30 to 50 mg/kg/day divided into 2 doses	B	Clostridium difficile infection	Hepatotoxicity, QT prolongation, hypertrophic pyloric stenosis (children), toxic epidermal necrolysis, pancreatitis, interstitial nephritis
Clarithromycin	PO	500 mg BID	15 mg/kg/day divided into 2 doses	C	Risk of congenital malformation. Clostridium difficile infection	Hepatotoxicity (elevated liver enzymes, hepatitis), QT prolongation
Levofloxacin	PO or IV	750 mg QD	Children >50 kg and >6 months: 500 mg QD. Children <50 kg and <6 months: 8 mg/kg BID	C	Tendinitis and Achilles tendon rupture. Anaphylactic reaction. Clostridium difficile infection	Agranulocytosis, thrombo-cytopenia, hepatotoxicity, seizures, depression, peripheral neuropathy, QT prolongation
Fosfomycin	PO	3 g QD (sachet)	Same adult dose in children over 12 years Children under 12 years not recommended	B	Clostridium difficile infection	Angioedema, aplastic anemia, asthma (exacerbation), cholestatic jaundice, liver necrosis, toxic megacolon
Rifampicin	PO	10 mg/kg/day QD	10 mg/kg/day QD	C	Postnatal hemorrhage. Clostridium difficile infection	Hepatotoxicity (hyperbilirubinemia, hepatocellular damage), DIC, leukopenia, hemolytic anemia, menstrual problems, anaphylaxis
Vancomycin	IV	500 mg every 6 hours or 1 g BID (concentration 5mg/ml pass 10 mg/min)	10 mg/kg every 6 hours (concentration 5 mg/ml pass 10 mg/min)	C	Hypotension, shock, and cardiac arrest with rapid administration. Clostridium difficile infection	Acute renal failure, ototoxicity, anaphylaxis, eosinophilia, exfoliative dermatitis, epidermal toxic necrolysis, vasculitis
Topical antibiotics						
Mupirocin	Topical	Application in affected areas 3 times a day for 10 days, cover with gauze		B	Clostridium difficile infection	Anaphylaxis, secondary wound infection, ulcerative stomatitis, angioedema, generalized rash
Fusidic Acid / Fusidate	Topical	Local application with or without dressing, once or twice a day, after cleaning the infected surface		B	NR	Contact dermatitis, eczema
Antivirals						

Acyclovir	PO	400 to 800 mg, 5 times a day for 7 to 10 days	Children <40 kg and >2 years: 20 mg/ kg per dose 4 times a day for 5 days. Children >40kg adult dose	B	Maintain adequate hydration due to kidney toxicity	Anaphylaxis, aggressive behavior, decreased consciousness, encephalopathy, epidermal toxic necrolysis, kidney failure
	IV	5 mg/kg pass in 1 hour, TID for 7 days	Children from 3 months to 12 years: 10 mg/kg pass in 1 hour, TID for 7 days			
Valaciclovir	PO	1 g TID for 7 days	20 mg/kg TID for 5 days. Maximum 1 g TID	B	Maintain adequate hydration due to kidney toxicity	Thrombotic thrombo-cytopenic purpura, hemolytic uremic syndrome, acute renal failure, CNS effects
Antifungals						
Itraconazole	PO	200 mg TID for the first 3 days, then 200 mg QD	3 to 5 mg/kg QD	C	Contraindicated in congestive heart failure.	Anaphylaxis, hepatotoxicity, dysrhythmias, ventricular dysfunction, pulmonary and peripheral edema, hearing loss
Fluconazole	PO or IV	Initial dose : 200 mg QD. Maintenance dose : 100 mg QD.	Initial dose : 6 mg/kg QD. Maintenance dose 3 mg/kg QD	D	Risk of congenital malformations	Anaphylaxis, skin exfoliative disorders, QT prolongation, dizziness, seizures, hepatotoxicity

Abbreviations: AD - atopic dermatitis; BID - twice a day; CNS - central nervous system; DIC - disseminated intravascular coagulation; IM - intramuscular; IV - intravenous; NR - not reported; PO - orally; QD - every day; TID - three times a day.
Source: Created from the FDA technical data sheets for each of the drugs[38,39,48–57,40,58,59,41–47]

Other biological agents

There are several other biologic drugs to mention with an appropriate efficacy in AD. *Nemolizumab* is a humanized monoclonal antibody that acts against the IL31 receptor A (2). It is currently in phase 3 clinical research for the treatment of moderate to severe AD. Nemolizumab has been shown to improve pruritus and clinical signs of AD but with less efficacy than other biological agents under study (1,2).

Tralokinumab is a monoclonal anti-IL13 antibody (2). The drug is currently in phase 3 clinical investigation and reported clinically significant changes in the severity of AD with a high-dose regimen along with topical corticosteroids versus placebo (16). Other promising agents in development for AD are lebrikizumab/anti-IL13, fezakinumab/anti-IL22, tezepelumab/stromal thymic lymphopoietin, mepolizumab/anti-IL5, omalizumab/Ig E and ustekinumab/anti-IL12 (26–33).

Janus kinase inhibitors

The pathophysiology of AD includes the JAK (Janus kinase)-STAT (signal transducer and activator of transcription) pathways that promote the signaling of various cytokines (IFN-γ, IL-4, IL-13, IL-31, IL-33, IL-23, IL-22, IL-17) favoring inflammation and involvement of the skin barrier. JAK inhibitors target different groups of kinases to decrease the severity and symptoms of AD (34).

Tofacitinib was the first JAK inhibitor (JAK 1, JAK 2, and JAK 3) tested in humans to be FDA approved in rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis (34). Tofacitinib was studied in 6 patients with moderate to severe AD refractory to treatment and achieved a 69% of reduction of the SCORAD (atopic dermatitis index) ($P<0.005$) and no AEs were evidenced (14).

Baricitinib is an FDA approved JAK 1 and JAK 2 inhibitor for rheumatoid arthritis (34). Baricitinib has a publication of two independent, multicenter, double-blind, phase III studies published in the British Journal of Dermatology (2020). The study reported at 16-

week of follow-up an improvement of the IGA (Investigator's Global Assessment) scale versus placebo (P<0.001) as well as improved quality of life, skin pain, and sleep interruptions (P≤0.05) versus placebo (35).

Ruxolitinib is a potent JAK1/JAK2 inhibitor approved by the FDA for the management of polycythemia vera and myelofibrosis. In AD, phase II studies with significant favorable results were reported improving EASI versus a vehicle cream regardless of the dose administered (P<0.001) (34).

Abrocitinib is a specific JAK1 inhibitor that continues to be studied for moderate to severe AD. A phase IIb study of abrocitinib reported a decrease in pruritus and an improvement in EASI and IGA (34).

Other JAK inhibitors being studied include upadacitinib, cerdulatinib, delgocitinib, ASN002, and SNA-125. However, limited evidence of their use in AD is available.

Adjuvant therapy options for complication

Systemic complementary treatments in AD described below are for those in charge of the management of pruritus with antihistamines and serious dermal infections with antimicrobials (8,14).

Antihistamines

Pruritus is a symptom that significantly affects the quality of life of AD patients and negatively impacts the dermatitis, infections, eye complications and quality of sleep (5).

Oral antihistamines block the histamine type 1 (HR1) receptors and have been prescribed in AD for decades even though their efficacy is controversial (1,11). First-generation antihistamines had significant sedative effects compared to second-generation antihistamines, so they should be used under surveillance and for a short time (5,11). The criteria for choosing between sedating or non-sedating antihistamines will depend on various aspects such as associated comorbidities (e.g. allergic rhinitis, bronchial asthma), the disease severity, sleep impairment and budget (11,14). The use of sedative antihistamines during pregnancy is not recommended. By contrast, cetirizine and loratadine can be used with caution and discretion. H1 antihistamines are classified as B category by the FDA (8). Antihistamines alone in the treatment of AD are not recommended because of the lack of valid evidence for their efficacy without combination with anti-inflammatory topical drugs (19).

Table 4 presents the classification of antihistamines according to their sedative effect and recommended dose (5).

Antimicrobials

Microorganisms play an important role in the pathophysiology of AD, the most important agents are staphylococcus, streptococcus, herpes simplex virus, molluscum contagiosum, human papillomavirus, and Malassezia furfur. Antibiotic therapy however is not recommended in all AD patients (11). The benefits, risks and indications regarding the use of antibiotics, antivirals and antifungals in AD described hereafter are summarized in Table 5.

Antibiotics

According to the European guidelines (2018), up to 90% of patients with AD present colonization by staphylococcus aureus and may remain asymptomatic. However, this microorganism can infect the skin and exacerbate the symptoms (14). Systemic antibiotics are recommended for short courses when signs of skin infection are present. The Brazilian guidelines (2019) recommended cephalosporins as the first line treatment, followed by trimethoprim sulfamethoxazole, while the European guidelines only mention cephalosporin as the first line treatment (1).

Antivirals

Viral infections are more frequent in AD patients than in the general population and increase the risk of dissemination Eczema herpetiformis and Kaposi's varicelliform rash are viral infections caused by the herpes virus and they are serious complications of AD which require immediate medical resolution (14,36). In cases of localized viral infection, oral acyclovir or valaciclovir is recommended, while in cases with altered general condition (fever, lethargy, headache, nausea, dizziness), hospitalization and intravenous administration of acyclovir could be necessary (1).

Antifungal

Antifungals treatment is recommended in patients with AD localized in the head and neck. In addition, patients who also present sensitization mediated by IgE against Malassezia spp should be treated (1,2). The most commonly systemic antifungals used in AD are itraconazole or fluconazole (2).

CONCLUSION

This review provides an evidence-based overview in the pharmacologic treatment options to treat AD. Discrepancies in guidelines may be due to differences in the prevalence of AD in these populations and the comorbidities of patients affected. All recommendations made here are the result of a consensus among a panel of experts in AD disease.

EXPERT OPINION

The pharmacologic management for AD is extensive and complex. Treatment decisions should be made in conjunction between doctor and patient to achieve high efficacy and patient satisfaction. Important factors for drugs selection should include patient desire for treatment, disease severity, socioeconomic context, and psychological status (17).

This work provides a global view about the topical and systemic pharmacological treatment options for children and adults with AD. Currently, several drugs are available on the market, some under development and others already approved by FDA and EMA. Some drugs are routinely used off-label, showing the importance to implement a management protocol for AD treatment. Pharmacological treatment is used to control the disease and treat complications. Since limited evidence is available with complete information of drugs, dosage, efficacy, and safety profile for AD treatment, we summarized AD treatment recommendations and therapies. However, updated guidelines for specific patient populations, such as pediatric patients, pregnant women, people with specific comorbidities, HIV, and the elderly may need to be published in a near future.

Several guidelines were reviewed and most of them agree that AD comprehensive management must include patient education, preventive strategies, phototherapy, and topic or systemic drugs. The choice between them depends mainly on the type of patient (child or adult) and the severity of the disease. The SCORAD index for severity evaluation before the treatment implementation was recommended by the experts. Topical drugs in AD treatment are also important because they have many benefits (e.g., being less invasive), can be used locally, and present fewer AEs compared to systemic approaches. Some indications for topical drugs may include mild to moderate AD, for local control of disease relapses and as preventive strategies in “hot areas”. Less than 10% of AD cases can be regarded as severe and will need stronger strategies with systemic therapies. The treatment options for patients with moderate-to-severe AD who do not respond to topical treatments have been suboptimal and poorly documented. By contrast, systemic therapies are in constant development but not always available in all countries (e.g., Crisaborole). The safety and efficacy of crisaborole were evaluated but its use by experts was not possible.

We identified major gaps in the research, such as the lack of references about the safety profile and dosages of drugs available for AD treatment. Guidelines weaknesses were also evidenced for a pharmacological treatment in children and adult AD populations that gathered all medications with dosage, duration, AEs, and management of complications. Several new drugs are on the market every day that limit an updated document of reference for the pharmacological treatment. Finally, many drugs are not available in all countries.

The main strength of this review was the updated evidence in the therapeutic area for AD management in children and adults. Limitations in the international references included lack of treatment options for children and adults simultaneously, ambiguous definition (age ranges) and no specific documents for

treatment in the adolescent population. In addition, the limited information regarding antimicrobial and biological drugs regarding treatment of AD was underscored due to lack of consensus regarding AD management application. The present document can be adapted according to the availability of drugs on the market.

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DECLARATION OF INTEREST

The authors declare that they have no competing interests.

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