



REVIEW

# National Saudi Consensus Statement on the Management of Atopic Dermatitis (2021)

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## ABSTRACT

Atopic dermatitis (AD) is a chronic inflammatory skin disease with an increasing prevalence regionally and globally. It is characterized by intense itching and recurrent eczematous lesions. With the increase in the availability of treatment options for healthcare practitioner and patients, new challenges arise for treatment selection and approach. The current consensus

statement has been developed to provide up-to-date evidence and evidence-based recommendations to guide dermatologists and healthcare professionals managing patients with AD in Saudi Arabia. By an initiative from the Ministry of Health (MOH), a multidisciplinary work group of 11 experts was convened to review and discuss aspects of AD management. Four consensus meetings were held on January 14, February 4, February 25, and March 18 of 2021. All consensus content was voted on by the work

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group, including diagnostic criteria, AD severity assessment, comorbidities, and therapeutic options for AD. Special consideration for the pediatric population, as well as women during pregnancy and lactation, was also discussed. The present consensus document will be updated as needed to incorporate new data or therapeutic agents.

**Keywords:** Consensus; Atopic dermatitis; Saudi Arabia

### Key Summary Points

Following recent advances in therapeutic development and increase in the availability of treatment options for atopic dermatitis, new challenges arise for treatment selection and approach

The aim of this article is to provide up-to-date evidence and evidence-based recommendations to guide dermatologists and healthcare professionals managing patients with atopic dermatitis in Saudi Arabia

The consensus development process was undertaken by a multidisciplinary work group of 11 experts, including six dermatologists and five pharmacists

Treatment goal of atopic dermatitis: EASI  $\geq$  75 response and NRS ( $<$  4) or DLQI  $\leq$  5

## INTRODUCTION

### Background and Definition

Atopic dermatitis (AD) is a chronic inflammatory dermatological disease affecting around a quarter of the pediatric population and 5–10% of adults worldwide [1–4]. The prevalence rates of AD among adults in different provinces of Saudi Arabia ranges from 6% to 13% [5].

Characterized by severe itching and recurrent eczematous lesions, its pathogenesis combines genetic susceptibility, skin barrier dysfunction, and immune dysregulation [6–9]. The clinical manifestations of AD vary with age, where area of involvement is the main differentiating factor. In infants (less than 2 years of age), lesions usually emerge on the cheek, forehead, scalp, neck, trunk, and extensor (outer) surfaces of the extremities. In children (2–12 years), adolescence, and adulthood, the flexural surfaces of the extremities are frequently affected [10].

### Purpose, Aim, and Scope

The management of AD encompasses various factors and can be variable between healthcare providers in daily clinical practice. As a result of the heterogeneity of the disease and regional treatment accessibility, notable diversity exists across international guidelines regarding the recommendations for the management of AD. With this in mind and following recent advances in therapeutic development and evidence-based recommendations, the current consensus recommendations were developed to provide guidance to dermatologists and healthcare workers, allowing them to ensure safe and satisfactory management of AD for their patients in Saudi Arabia. Topics reviewed in this document include diagnostic criteria, AD severity assessment, comorbidities, and treatment options. Special considerations for the management of AD in the pediatric population, as well as women during pregnancy and lactation, and vaccination in patients with AD were also discussed. These recommendations are intended to support rather than replace physician's clinical judgement.

### Disclaimer on the Use of Clinical Practice Guidelines

Clinical practice guidelines are based on the best information available at the time of writing and are to be updated regularly. They are evidence-based tools for guiding physicians managing health conditions. They are not fixed protocols and strict treatment guidelines that

must be followed but are only tools to help manage AD patients. Decisions pertaining to treatment must be taken on a case-by-case basis tailoring the treatment regimen to patients' personal circumstances and medical history. Physicians are advised to consult approved product monographs in their institution's formulary. These formularies include drug dosage, special warnings precautions for use, contraindications, and side effects. Physicians should consider institutional formulary restrictions when selecting treatment options.

### Target Population, Audience/End Users

The target population for the present consensus document is pediatric and adult people with AD. The targeted audience/end users are general dermatologists and other healthcare providers who encounter patients with AD in secondary and tertiary care settings.

## METHODS

A multidisciplinary work group of 11 experts, including six dermatologists and five pharmacists, was chosen on the basis of their experience in treating AD. One method expert was invited and consulted throughout the process of developing the consensus recommendations. The Saudi Ministry of Health (MOH) oversaw and supported the process. Four consensus meetings were held on January 14, February 4, February 25, and March 18 of 2021.

During the first meeting, the work group defined the objectives, scope, target population, and target audience of the consensus statements. The work group identified four main topics of interest, which would serve as the sections for review: (1) diagnostic criteria, (2) AD severity assessment, (3) evaluation and treatment of comorbidities, (4) management of AD and treatment options. Work group members were assigned to one of these four workstreams depending on their interest and expertise and developed content for the document within their respective sections.

The work group identified seven international guidelines for AD management that

served as the basis for the generation of the current guidelines: the 2017 and 2020 European guidelines, the 2017 and 2020 Japanese guidelines, the 2014 and 2017 American guidelines, and the 2019 Indian guidelines [3, 7, 11–17]. The literature review and reference lists from the identified guidelines and consensus statements were then evaluated to locate additional articles.

A draft of the developed content was circulated among group members prior to the second and third meetings. During the meetings, consensus was reached using the nominal group technique after thorough discussions. All work group members had the right to vote on the recommendations. When agreement was achieved by at least 75% of the voting experts, the statement was considered consented, but strength of recommendation was not addressed.

All the consented recommendations were shared with the MOH and work group experts for any further input. A final workshop for the work group was then held in March 2021 to discuss the additional input for further agreement. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

## DIAGNOSTIC CRITERIA

AD is a clinical diagnosis based on characteristics of morphology, age-dependent distribution, and associated clinical signs. Various criteria for diagnosis have been proposed over the years to maximize the accuracy of diagnosis. We recommend using the criteria developed by the American Academy of Dermatology for definite diagnosis (Table 1) [3].

## ATOPIC DERMATITIS SEVERITY ASSESSMENT

Defining and assessing disease severity is essential in directing treatment choices in AD. Because there are no serologic markers that precisely reflect AD, measurement of severity is primarily based on signs and symptoms. Several

**Table 1** Features to be considered in the diagnosis of patients with atopic dermatitis

<i>Essential features</i>	Pruritus
Must be present	Eczema (acute, subacute, chronic)
	Chronic or relapsing history
	Typical morphology and age-specific patterns
	Facial, neck, and extensor involvement in infants and children
	Current or previous flexural lesions at any age
	Sparing of the groin and axillary regions
<i>Important features</i>	Early age of onset
Seen in most cases, adding support to the diagnosis	Atopy
	Personal and/or family history
	IgE reactivity
	Xerosis (dry skin)
<i>Associated features</i>	Atypical vascular responses
Suggest the diagnosis but are too nonspecific to be used for defining or detecting AD for research studies	Facial pallor, white dermographism, delayed blanch response
	Keratosis pilaris/pityriasis alba/hyperlinear palms/ichthyosis
	Ocular/periorbital changes
	Other regional findings
	Perioral/periauricular lesions
	Perifollicular accentuation/lichenification/prurigo lesions
<i>Exclusionary conditions</i>	Such as:
A diagnosis of AD depends upon excluding other conditions	Scabies
	Seborrheic dermatitis
	Contact dermatitis (irritant or allergic)
	Ichthyosis
	Cutaneous T cell lymphoma
	Psoriasis
	Photosensitivity dermatoses
	Immune deficiency diseases
	Erythroderma of other causes

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physician- and patient-rated severity assessment tools are available, varying considerably with respect to content, scale, instructions, validity, and concordance. These include the SCORing Atopic Dermatitis (SCORAD) index, the Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM), Physician Global Assessment (PGA), body surface area (BSA), Dermatology Life Quality Index (DLQI), and pruritus Numerical Rating Scale (NRS).

In terms of the practical applications of these assessment tools, we recommend using PGA, EASI, pruritus NRS, and DLQI, as they are practical tools for use in routine clinical practice, widely recognized by local health authorities, and capture the essential elements of the disease.

## COMORBIDITIES OF ATOPIC DERMATITIS

AD is associated with multiple atopic and non-atopic comorbidities [18]. There is a bidirectional and multifactorial relationship between AD and these comorbidities. Some of these comorbidities could be secondary to the burden of chronic AD or distinct pathomechanisms triggered by AD. To improve outcomes and clinical decision-making for patients with AD, important consideration must be given to comorbidities [18].

### Atopic Comorbidities

According to the American Academy of Dermatology, atopic comorbidities like asthma, allergic rhinitis/rhinoconjunctivitis, and food allergy are diagnostic criteria for AD [3]. However, there is some controversy regarding the mechanisms and epidemiology of these comorbidities in AD [18]. Studies have shown that AD was statistically significantly associated with a higher prevalence of these atopic comorbidities in comparison to population-based controls without AD [19]. Among children with more severe AD, the severity and prevalence of these comorbidities are greater [20]. Asthma prevalence increases with

worsening AD [21]. While AD severity is the strongest predictor, other characteristics were found to be related to atopic comorbidities in adult patients with AD [22].

In addition to that, eosinophilic esophagitis (EOE), which is a rare disease, is more prevalent in AD and is recognized as a comorbidity of AD [23].

The progression of atopic disorders, from eczema in infants and toddlers to allergic rhinitis and finally to asthma in older toddlers and children, is referred to by the term “atopic march” [24]. EOE has been recently recognized as a late manifestation of the atopic march in pediatric patients [24, 25]. These conditions seem to be interconnected. Nevertheless, their relationship is still not thoroughly explored and is less likely to be that of progression particularly because of the different genetic and environmental factors playing a role in the atopic march [26].

Developing different atopic comorbidities in younger children with AD was found to be associated with disease severity, age at onset, atopic history in parents, filaggrin (FLG) mutations, polysensitization, and nonrural environment [27].

### Other Comorbidities

#### *Allergic Contact Dermatitis*

Allergic contact dermatitis (ACD) may be more common in patients with AD than in the general population [28, 29]. Secondary to barrier disruption, patients with AD have greater absorption of irritants and allergens through the skin. This leads to immune activation and ultimately contact sensitization [29–33]. Patients with AD regularly use topical corticosteroids and emollients that contain contact sensitizers like propylene glycol and sorbitan [29, 33–36]. Avoidance of contact allergen and confirming the diagnosis with patch testing are advised in selected cases [37].

#### *Behavioral and Mental Health Conditions*

Intense pruritus, high sleep disturbance rates, stigma, social isolation, poor quality of life (QoL), and neuro-inflammation have been

postulated to contribute to increased anxiety, depression, suicidality, or attention deficit hyperactivity disorder (ADHD) in AD [18]. Depression was usually present in moderate-to-severe AD with depressive symptoms directly correlated with disease severity and modifiable with improved AD treatments [38].

### **Infections**

AD is frequently complicated by cutaneous and extracutaneous infections. Cutaneous infections are related to immune dysregulation, skin-barrier dysfunction, lower antimicrobial peptides, increased bacterial colonization, and use of immunosuppressive medications [39]. Studies have found that 70% of patients with AD were colonized with *Staphylococcus aureus* on lesional skin, 39% on the non-lesional skin, and 62% in the nose [40]. Systemic antibiotics should only be used if skin is clinically infected, and not because there is a positive culture of *S. aureus* [40]. In severe disease, there are strong correlations between AD and eczema herpeticum (EH) [41].

AD is also associated with a higher risk of extracutaneous infections, such as upper respiratory tract infections, pneumonia, recurrent ear infections, sinus infections, gastroenteritis, urinary tract infections, and higher usage of antibiotics in children with AD compared with healthy controls [42, 43]. Consider infection risk in clinical decision-making for patients with AD. For example, a history of recurrent infections may raise suspicion for an underlying immune deficiency [39, 44].

### **Cardiometabolic Comorbidities**

AD is associated with a greater risk of cardiovascular disease and events, particularly in severe AD. There are multiple potential risk factors for cardiometabolic disease among patients with AD, including sleep disturbance [43, 45], sedentary lifestyle [46], obesity, higher rates of cigarette smoking [47], and side effects from some systemic medications (e.g., corticosteroids and cyclosporine A).

Patients with AD are at higher risk of suffering from hypertension, coronary artery disease,

heart attack, congestive heart failure, peripheral vascular diseases, and stroke [48].

## **MANAGEMENT OF ATOPIC DERMATITIS**

### **Eligibility Criteria for Systemic/Biologic Treatment**

Systemic treatments are generally indicated in moderate-to-severe AD. Based on the recommended clinical scoring tools, at least one of the following criteria can be used to define moderate-to-severe AD and are considered as appropriate criteria for initiating systemic therapy [15, 49–52]:

1. EASI  $\geq 16$
2. DLQI score  $\geq 10$
3. Pruritus NRS  $\geq 4$
4. PGA  $\geq 3$
5. BSA score  $\geq 10\%$

### **Atopic Dermatitis Treatment Goals**

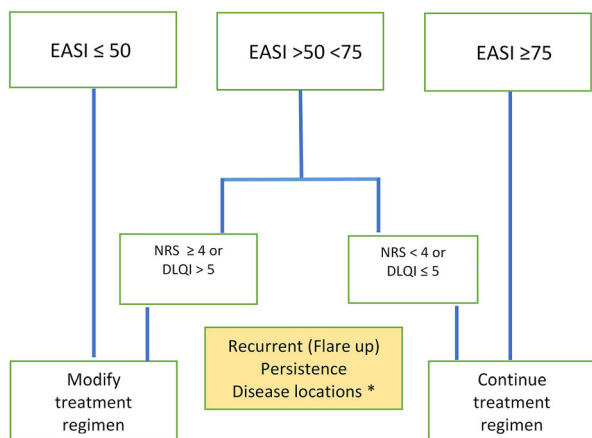
In general, the goal of treatment is to decrease skin inflammation and pruritus, restore skin barrier function, and enhance QoL. It is advisable to define goals of treatment for every patient ahead of initiating treatment. EASI, PGA, DLQI, and NRS are recommended for use in daily practice to establish and monitor the achievement of treatment goals and guide therapy (Fig. 1). We recommend that both the following criteria should be achieved for the treatment goal of AD within 16 weeks [7, 49]:

1. EASI  $\geq 75$  response
2. NRS ( $< 4$ ) or DLQI  $\leq 5$

For Saudi MOH regulatory requirements and for the purposes of payer reimbursement, the EASI tool is required.

### **Patient Education**

Educating patients and caregivers in AD has proved to increase adherence to treatment, promote better outcomes, and improve QoL



**Fig. 1** Atopic dermatitis treatment goals. \*Recurrence (flare-up), persistent disease, and disease location are factors to be taken into consideration when determining moderate-to-severe disease

[53–55]. Different educational programs have been studied, and their structure depends on the social and economic conditions [56]. However, the main principles of these programs revolve around the following:

### Emollients

In AD, the function of the skin barrier including moisturizing factors is impaired, leading to invasion of allergens which trigger dermatitis flares. Topical moisturizers suppress itching and help in maintaining skin barrier function [57].

As a result of the risk of contact allergies, emollients with the least number of ingredients are recommended. Fragrances and preservatives which may contain known allergens should be especially avoided [58]. Special consideration should be given to emollients containing allergic plant proteins from peanut, oat, or wheat and must be avoided in children less than 2 years of age [59].

Liberal amounts of emollients should be applied. Moisturizing twice-daily (morning and evening) and after bathing (soak and seal technique) are the most effective [7, 15].

Continuous usage of moisturizing products after dermatitis remission with topical anti-inflammatory drugs is evident for maintaining the remission [60].

### Cleansing

In AD, adhesion of body fluid (sweat), topical drugs, sebum, and bacterial contaminants may have a role in exacerbating the diseases. Keeping the skin clean is essential in maintaining the physiologic properties of the skin. However, this should be done with low-irritant, nonallergenic formulas with the least additives like pigment and perfumes and should be rinsed thoroughly to protect the skin from irritation [7, 15].

The frequency of showering showed no difference between twice weekly or every day in a small, randomized study as long as the skin's hydration is managed after the bath [61]. However, prolonged showers should be avoided as they are associated with worsening of symptoms [62]. Water temperature should be set between 37 and 38 °C as this is the optimum temperature for skin barrier recovery, and higher temperatures induce itching response [63–65].

Intermittent use of antiseptic baths can be considered in patients with recurrent skin infections. An example is the addition of one-quarter to one-half cup of 6% household bleach in a bathtub full of water (40 gallons) [66]

### Aggravating Factors

It is fundamental to educate patients and families about exacerbating factors; these may include:

**Nonspecific Irritation** Contact with sweat, saliva, hair, and friction against clothes may exacerbate AD symptoms. Appropriate measures should be taken to avoid nonspecific irritation. For example, sweat and saliva should be washed or wiped away, nonirritating clothing should be chosen (rough textured clothes like wool must be avoided), and hair should be tied up to reduce itching [15].

Scratching is also an important exacerbating factor. In addition to therapeutic measures to control pruritus, education about cutting nails short, wearing long sleeves and long pants may reduce scratching practices [15].

**Contact Allergy** Progression of AD can be caused by contact with cosmetics, perfumes,

metals, topical drugs, plants, and skin and hair care products. Suspicion of contact allergy should be raised in cases where AD onset and worsening has occurred recently with limited response to treatment or with atypical eczema distribution [37].

**Food Allergen** Associated food allergy is present in one-third of children with moderate-to-severe AD [67]. Among infants and toddlers, risk of AD exacerbation is higher with Cow's milk, hen's egg, wheat, soya, tree nut, and peanuts. On the other hand, in older children and adults, pollen-related food allergens are mostly associated with AD exacerbations [68]. Food elimination should be undertaken only when there is clear evidence of food allergy as this can affect child development. When suspecting food allergy, referral to allergist-immunologist should be considered.

**Aeroallergen** Aeroallergens (mites, house dust, pollen, pet hair) are relevant trigger factors for AD diagnostic workup includes skin prick tests or serum Immunoglobulin E antibody tests. Conversely, both methods have a low predictive value. Avoidance of aeroallergen should be based on careful evaluation of any changes in eruption features or environmental factors. Due consideration should be given for the individual's medical history and results of elimination and challenge tests [15].

## Pharmacologic Therapies

### Topical Therapies

**Topical Anti-inflammatory Therapies** Topical corticosteroids (TCSs) are considered the mainstay of AD therapy and have been used for decades. They are used as a first-line anti-inflammatory treatment option in AD. TCSs are classified into four classes according to their potency (Table 2) [17].

The potency and vehicle of the TCSs should be tailored on the basis of consideration of different factors, including the patient age, body area involved, disease severity, and treatment duration [69]. Twice-daily application of TCSs is advised for AD treatment. Clinical trials have

**Table 2** Classification of topical corticosteroids and registration status in Saudi Arabia

Class, potency	Generic name	Strength	SFDA registration
Class I, very potent	Clobetasol propionate	0.05%	Approved
	Beclometasone dipropionate	0.025%	Approved
Class II, potent	Betamethasone valerate	0.1%	Approved
	Betamethasone dipropionate	0.05%	Approved
	Diffucortolone valerate	0.1%	Approved
	Fluocinolone acetonide	0.025%	Approved
	Hydrocortisone butyrate	0.1%	Approved
	Mometasone furoate	0.1%	Approved
Class III, moderate	Triamcinolone acetonide	0.1%	Approved
	Alclometasone dipropionate	0.05%	Not approved
	Betamethasone valerate	0.025%	Approved
Class IV, mild	Clobetasone butyrate	0.05%	Approved
	Fluocinolone acetonide	0.00625%	Approved
	Hydrocortisone	0.1–2.5%	Approved
	Fluocinolone acetonide	0.0025%	Approved

shown that TCSs are safe and effective for treating AD flare-ups when used for up to 4 weeks [70]. However, many flare-ups may be adequately controlled with a shorter treatment course (1–2 weeks) [71]. In clinical practice,



other medications are used in combination with TCS.

For maintenance therapy, TCSs and emollients should be used proactively (e.g., intermittent, or twice-weekly dosing) for up to 16 weeks and are effective in reducing the risk of flares [72, 73]. Cutaneous and systemic side effects can occur, particularly with very potent and potent TCS (classes I and II) [74]. Patients using TCS over the long-term should be monitored by regular physical examinations to monitor for cutaneous side effects [75]. Very potent TCS (class I) are not recommended for AD treatment, especially in children.

Topical calcineurin inhibitors (TCIs) (tacrolimus and pimecrolimus) are indicated as second-line anti-inflammatory treatment option for moderate-to-severe AD (tacrolimus) and in mild-to-moderate AD (pimecrolimus) in adults and children at least 2 years of age when other topical therapies are inadequate or inadvisable [76, 77]. They can be used off-label as first-line therapy in selected cases, particularly in sensitive skin areas, and in patients receiving long-term therapy [7]. TCSs can be combined with TCI for the treatment of AD [7].

Proactive, intermittent therapy with tacrolimus twice weekly for up to 52 weeks is effective in preventing, delaying, and reducing the occurrence of flares, thus improving QoL for patients with AD [78, 79].

Transient burning or stinging sensation is common when using TCIs and may be associated with the initial application and improve with continued use (Table 3) [76, 77].

**Topical Phosphodiesterase 4 (PDE4) Inhibitors** Crisaborole is indicated for the treatment of mild-to-moderate AD in adults and pediatric patients 3 months or older [80]. It inhibits PDE4, resulting in an increase in intracellular cyclic adenosine monophosphate, which causes reduction in pruritogenic cytokines production [80, 81]. On the basis of two pivotal phase III clinical trials done on patients aged 2 years or older, as compared with vehicle only, crisaborole significantly increased Investigator's Static Global Assessment score of clear or almost transparent with a two-grade or more remarkable improvement from baseline and

improved all signs of AD like erythema, exudation, excoriation, induration, and lichenification [81] (Table 3).

**Novel Topical Therapies** Delgocitinib ointment is a topical JAK (Janus kinase) inhibitor approved in Japan for treating adult patients with moderate-to-severe AD for up to 28 weeks, and other topical JAK inhibitors (topical tofacitinib and ruxolitinib) seem to be promising treatments for mild-to-moderate AD in a phase II, randomized trial [82].

### **Phototherapy**

Phototherapy is an adjuvant skin-directed therapy, thus reducing sleep disturbances in patients with AD [83]. It is considered, with concomitant topical anti-inflammatory therapies, as an acceptable treatment choice for moderate-to-severe AD, if available. It can also be used as monotherapy for patients in whom topical anti-inflammatory therapies are not appropriate (i.e., adverse reaction, contraindication) [84].

Ultraviolet A1 (UVA1) and narrow-band ultraviolet B (NB-UVB) are the most appropriate phototherapy options for AD treatment [84]. Actinic damage, local erythema and tenderness, pruritus, burning, and stinging are common adverse events of phototherapy [85–87].

In practice, phototherapy's limitations are accessibility, feasibility, and lack of efficacy on lesions on the scalp and folds. Concomitant treatment with topical anti-inflammatory drugs, emollients, and phototherapy are appropriate options to decrease the frequency of flare-ups [13, 88].

### **Systemic Therapies**

If AD cannot be controlled adequately with appropriate topical treatments and phototherapy, systemic therapy is recommended. It is helpful in patients who usually require potent TCS for large body areas over extended periods of time. Systemic treatment options for AD include systemic corticosteroids, cyclosporine A (CsA), azathioprine (AZA), mycophenolate mofetil (MMF), and methotrexate (MTX) (Tables 4, 5).

**Table 3** Topical calcineurin inhibitors and topical phosphodiesterase 4 inhibitors for treatment of atopic dermatitis

Drug name	Pharmacological category	SFDA registration	FDA approved	Adult dose	Pediatric dose	Pregnancy category	Relapse	Medication safety	
								Adverse effects	Black box warning
Crisaborole [80]	(PDE4)	No	Yes	Apply twice daily	3 months or older: apply a thin layer twice daily	Fetal risk cannot be ruled out	7–29 days	Hypersensitivity reaction, site pain	No
Pimecrolimus [76]	TCI	Yes	Yes	Apply 1% cream topically to affected areas twice daily	2 years or older: apply 1% cream thin layer twice daily	Fetal risk cannot be ruled out	6 weeks	Headache, persistent erythema of skin, burning, pruritus, rash, discoloration of skin	Malignancy (e.g, skin, melanoma, and lymphoma)
Tacrolimus [77, 115]	TCI	Yes	Yes	Apply thin layer of 0.03% or 0.1% ointment topically to affected areas twice daily	2–15 years: apply thin layer of 0.03% ointment topically to affected areas twice daily	Fetal risk cannot be ruled out	6 weeks	Persistent erythema of skin, burning, pruritus, rash	

TCI topical calcineurin inhibitor, PDE4 phosphodiesterase 4, FDA

Systemic corticosteroids: long-term systemic steroid should be avoided. However, it can be used for short courses to treat an acute exacerbation. Moreover, risk of a flare-up with discontinuation of the systemic steroid should be considered [14, 15, 89].

CsA is an oral calcineurin inhibitor used for moderate-to-severe AD. It is licensed for the AD treatment in adults in many European countries and may be used off-label in children and adolescent patients with a refractory or severe disease. The treatment duration could vary between 3 months and 1 year. Nevertheless, longer durations of low-dose CsA could be tolerated in some patients [7] (Tables 4, 5).

MTX is an immunosuppressive agent that is frequently used off-label to treat moderate-to-severe AD [14, 90]. Methotrexate has a slow onset of action, and its maximum effect is reached after 8–12 weeks of treatment [91, 92]. Other immunosuppressants including AZA and MMF can be used for moderate-to-severe AD treatment [14, 93–96] (Tables 4, 5).

In 2017, the US Food and Drug Administration (USFDA) and Saudi Food and Drug Authority (SFDA) approved dupilumab as the first biologic for patients with moderate-to-severe AD who are not optimally responsive to topical therapies or when those therapies are inadvisable or treatment failure on one or more oral immunosuppressive drugs in patients 6 years or older [97, 98].

Dupilumab is a fully human monoclonal antibody directed against the interleukin (IL)-4a receptor alpha-subunit. It works by blocking the signaling of two key drivers of type 2 immune response, namely IL-4 and IL-13 [97, 98].

Dupilumab should be combined with daily emollients with or without topical anti-inflammatory drugs as needed. Until the full clinical outcome is achieved, conventional systematic immunosuppressants could be continued during the first few weeks of initiating dupilumab [97, 98] (Table 6).

Combining dupilumab with a conventional drug or phototherapy is an appropriate and safe therapy option which allows patients recalcitrant to dupilumab monotherapy [99]. Subsequent real-life studies have confirmed the data from the registration studies in clinical practice,

**Table 4** Systemic therapies for treatment of moderate-to-severe atopic dermatitis

Immunosuppressant agent	Pharmacologic category	Authority approval	SFDA registration	Dosing in adult	Dosing in children	Time to reassessment (weeks) [116]	Time to relapse (weeks)
Cyclosporine [14, 117, 118]	Calcineurin inhibitor	FDA: off-label EMA: licensed	Yes	2–5 mg/kg/day	2–5 mg/kg/day	4	< 2
Methotrexate [11, 14, 90, 91]	Antimetabolite	FDA: off-label EMA: off-label	Yes	5–25 mg/week	0.2–0.7 mg/kg/week	12–16	> 12
Azathioprine [11, 14, 93–95]	Purine antimetabolite	FDA: off-label EMA: off-label	Yes	1–3 mg/kg/day	1–4 mg/kg/day	12	> 12
Mycophenolic acid [14, 96]	Antineoplastic antibiotic	FDA: off-label EMA: off-label	Yes	1–3 g/day	20–50 mg/kg/day	12	> 12

EMA European Medicines Agency, FDA US Food and Drug Administration, SFDA Saudi Food and Drug Authority

**Table 5** Safety of systemic therapies

Immunosuppressant agent	Monitoring		Adverse effects	
	Baseline	Follow-up	Common	Serious and rare
Cyclosporine	CBC/differential/platelets, LFT	CBC/ differential/platelets, LFT, RFT, TB testing <sup>b,d</sup> , HCG <sup>b</sup> , BP, lipid profile	Hypertension, tremor, hypertrichosis, headache	Hyperkalemia, hypomagnesemia encephalopathy, progressive multifocal leukoencephalopathy, seizure, hemolytic uremic syndrome, nephrotoxicity, infectious disease, skin cancer, and lymphoma
	fasting lipid profile, electrolytes (Mg, K), uric acid	Electrolytes (Mg, K) <sup>c</sup> , uric acid <sup>e</sup> , therapeutic drug monitoring		
Methotrexate <sup>a</sup>	CBC/differential/platelets, LFT	LFT <sup>f</sup> , RFT <sup>g</sup> , TB testing <sup>b,d</sup> , HCG <sup>b</sup>	Alopecia, photosensitivity, rash, abdominal pain, diarrhea, indigestion, nausea, stomatitis, vomiting, thrombocytopenia, LFT abnormal, headache, bronchitis, and nasopharyngitis	Thromboembolic disorder, erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis, agranulocytosis, aplastic anemia, leukopenia, pancytopenia, cirrhosis of liver, hepatic fibrosis, hepatitis, malignant lymphoma, opportunistic infection, leukoencephalopathy, seizure, renal failure, interstitial pneumonia, and pulmonary toxicity
	RFT, TB testing <sup>b</sup> , HCG <sup>b</sup> , HIV <sup>b</sup> , HBV/HCV, pulmonary function tests <sup>b</sup>			
Azathioprine	CBC/differential/platelets, LFT	CBC/ differential/platelets <sup>h</sup> , LFT <sup>h</sup> , RFT <sup>h</sup> , TB testing <sup>b</sup> , HCG <sup>b</sup>	Nausea, vomiting, bloating, anorexia, cramping, headache, hypersensitivity reactions, and elevated liver enzymes	Leukopenia, infection, lymphoma, pancreatitis, adenocarcinoma of lung, and nonmelanoma skin cancer
	RFT, TB testing <sup>b</sup> , HCG <sup>b</sup> , HIV <sup>b</sup> , HBV/HCV, TPMT <sup>c</sup>			

**Table 5** continued

Immunosuppressant agent	Monitoring		Adverse effects	
	Baseline	Follow-up	Common	Serious and rare
Mycophenolic acid	CBC/differential/platelets, LFT	CBC/differential/platelets <sup>c</sup> , LFT <sup>d</sup> , TB testing <sup>b</sup> , HCG <sup>b</sup> , HIV <sup>b</sup>	Hyperglycemia, edema, hypertension, abdominal pain, constipation, diarrhea, nausea, vomiting, headache, insomnia, serum blood urea nitrogen raised, and serum creatinine raised	Gastrointestinal hemorrhage, pleural effusion, leukopenia, neutropenia, pancytopenia, thrombocytopenia, and renal impairment

*BP* blood pressure, *LFT* liver function test, *RFT* renal function test, *TPMT* thiopurine methyltransferase level, *HCG* human chorionic gonadotropin, *HIV* human immunodeficiency virus, *UA* urinalysis, *HBI/HCV* hepatitis B virus, hepatitis C virus

<sup>a</sup>Folic acid supplementation is shown to decrease methotrexate side effects

<sup>b</sup>If clinically indicated

<sup>c</sup>If this *TPMT* test is not available, treatment can be started with half the dosage

<sup>d</sup>Annual testing

<sup>e</sup>Check laboratory results 2–4 weeks after an increased dose

<sup>f</sup>Weekly for 1 month, then every 2 weeks for 1 month, then every 2–3 months during therapy

<sup>g</sup>Every 6–12 months

<sup>h</sup>Twice monthly for 2 months, then monthly for 4 months, then every other month or if dose increases

<sup>i</sup>Every 2 weeks for 1 month, then monthly for 3 months, then every 2–3 months during the course of therapy

Table 6 New and developing therapies for atopic dermatitis

Drug name	Authority approval <sup>c</sup>	Dose	Efficacy at week 16		Pregnancy category	Safety	Monitoring			
			EASI-75	Improvement in IGA 0–1 DIQI score $\geq$ 4 points				Improvement in worst pruritus NRS $\geq$ 4		
Dupilumab <sup>a</sup> [97, 98, 119]	FDA: Yes EMA: Yes	<i>Adult:</i> SubQ Initial: 600 mg then 300 mg once every other week <i>Pediatric</i> <i>patients <math>\geq</math> 6 years</i> <i>of age:</i> Less than 30 kg: 600 mg then 300 mg once every month Less than 60 kg: 400 mg then 200 mg once every other week 60 kg or more: 600 mg then 300 mg once every other week	300 mg; 52%	300 mg; 64.1%	300 mg; 40.8%	300 mg; 37.9%	300 mg; 40.8%	Fetal risk cannot be ruled out	Injection site reactions, antibody development, conjunctivitis, blepharitis, oral herpes, and transient eosinophilia	Although as per SmPC, there is no required routine monitoring, the following is recommended as per expert opinion: <i>At week 0:</i> CBC, LFT, RFT, TB testing, HIV if indicated, HCG if indicated <i>At week 12:</i> Further laboratory monitoring according to routine patient management

**Table 6** continued

Drug name	Authority approval <sup>c</sup>	Dose	Efficacy at week 16		Improvement in worst pruritus NRS $\geq 4$	Pregnancy category	Safety	Monitoring
			EASI-75	DLQI score $\geq 4$ points				
Baricitinib <sup>b</sup> [103, 104, 116]	FDA: No EMA: Yes	Adult: 4 mg once daily	2 mg: 18.7%	2 mg: 18.6%	2 mg: 12%	Fetal risk cannot be ruled out	Headache, increased liver enzyme, herpes simplex, decrease neutrophil count, and nasopharyngitis	At week 0 CBC (platelet, Hgb), WBC (ALC, ANC), LFT, RFT TB testing, HIV if indicated, HCG if indicated, lipid parameters
		Aged $\geq 75$ years: 2 mg once daily	4 mg: 24.8%	4 mg: 40.9%	4 mg: 21.5%			
		Patients with creatinine clearance 30–60 mL/min: 2 mg once daily			16.8%			
Upadacitinib <sup>b</sup> [104, 105]	FDA: Yes EMA: Yes	Adult: 15 or 30 mg orally once daily	15 mg: 69.6%	15 mg: 75%	15 mg: 52%	Fetal risk cannot be ruled out	Respiratory infections, herpes simplex, worsening of AD, and acne	At week 4: Lipid parameters, CBC (platelet, Hgb), WBC (ALC, ANC), RFT, LFT
			30 mg: 79.7%	30 mg: 82%	30 mg: 60%			
Abrocitinib <sup>b</sup> [104, 107]	FDA: Yes EMA: Yes	Adult: 200 mg once daily for 12 months	At week 12	At week 12	At week 12	Fetal risk cannot be ruled out	Nasopharyngitis, nausea, herpes simplex, acne, creatine phosphokinase elevations, and headache	At week 12: Lipid parameters, CBC (platelet, Hgb), WBC (ALC, ANC), RFT, LFT
		Aged $\geq 65$ years: 100 mg once daily for 12 months	100 mg: 40%	100 mg: 20.2%	100 mg: 38%			
			200 mg: 63%	200 mg: 31.9%	200 mg: 57%			After week 12: Further laboratory monitoring according to routine patient management

Table 6 continued

Drug name	Authority approval <sup>f</sup>	Dose	Efficacy at week 16		Improvement in IGA 0–1 in worst pruritus NRS $\geq$ 4	Improvement in DLQI score $\geq$ 4 points	Pregnancy category	Safety	Monitoring
			EASI-75	DLQI					
Tralokinumab [120]	FDA: Yes EMA: Yes	Adult: 600 mg once, followed by 300 mg once every other week	33.2%	56.3%	22%	25%	Fetal risk cannot be ruled out	Atopic dermatitis flares, viral upper respiratory infections, injection site reactions, keratitis, and conjunctivitis	Although as per SmPC, there is no required routine monitoring the following is recommended as per expert opinion: <i>At week 0:</i> CBC, LFT, RFT, TB testing, HIV if indicated, HCG if indicated <i>At week 12:</i> Further laboratory monitoring according to routine patient management

CBC complete blood count, RFT renal function tests, LFT liver function tests, TB tuberculosis, HIV human immunodeficiency virus, HCG human chorionic gonadotropin, WBC white blood count, ALC absolute lymphocyte count, ANC absolute neutrophil count

<sup>a</sup>Pharmacologic category: interleukin-4 receptor antagonist

<sup>b</sup>Pharmacologic category: Janus kinase inhibitor

<sup>c</sup>All are registered in SFDA except for abrocitinib



regarding efficacy, safety, and improvement of patient-reported outcomes [100, 101]

The European Medicines Agency (EMA) and SFDA approved baricitinib and upadacitinib (JAK inhibitors) to treat moderate-to-severe AD in adult patients who are candidates for systemic therapy [102–106]. On the other hand, USFDA and SFDA approved upadacitinib to treat moderate-to-severe AD in pediatric patients at least 12 years of age and adults, and abrocitinib for adults only [104, 107] (Table 6). Tralokinumab is another fully human monoclonal anti-IL-13 antibody recently approved by the USFDA and EMA for treating moderate-to-severe AD that is not adequately controlled with topical prescription therapies for adults. It is not yet approved by the SFDA.

### ***New Treatment in the Pipeline***

Monoclonal antibodies that inhibit the effects of various interleukins (i.e., IL-4, IL13, IL-5, IL-17, IL-22, IL-31, IL-33) show therapeutic promise for the treatment of AD such as nemolizumab, lebrikizumab, and fezakinumab [108].

### **Treatment Algorithm**

The treatment algorithm for AD is shown in Fig. 2. Patients who fail first-line therapy or who have contraindications to these therapies are candidates for systemic therapies. Treatment failure may be considered as an inadequate response after 4–8 weeks of appropriate topical therapy with or without 12–16 weeks of phototherapy. Availability, suitability, and compliance to phototherapy should be considered [52, 71].

General response to most systemic therapies should be evaluated after 12 weeks, except for cyclosporine, where the response should be evaluated after 6 weeks. Dose optimization or switching should be considered if there is no improvement [71].

Reconsider diagnosis of AD for refractory cases/persistent cases despite optimum therapy.

Most of the guidelines do not prefer one systemic therapy over another. However, cost and safety should be taken into consideration [51].

### **Referral of Patients with Atopic Dermatitis**

Most patients with AD are responsive to dedicated conservative treatment. We recommend referral to a dermatologist in the following indications [109, 110]:

1. Same day referral
2. Suspicion of eczema herpeticum—urgent referral, ideally within 1–2 weeks
  - Severe AD irresponsive to optimal topical therapy is seen after 2–4 weeks
  - If treatment of bacterial-infected AD has failed
3. Routine (non-urgent) referral (ideally, every patient shall be seen within 1–4 weeks; however, it might take longer)
  - Diagnosis is uncertain.
  - Partially responded AD to the appropriate treatment and duration.
  - AD on face/genitalia/palms and soles which is suboptimally controlled or affecting the patient's QoL.
  - AD with history of severe and recurrent infections.
  - Contact allergic dermatitis is suspected.
  - Uncontrolled or poorly controlled AD subjectively.
  - AD responsive to optimal management but with non-enhancing QoL and psychosocial well-being must be referred for psychological advice.
  - Moderate or severe AD with suspected food allergy must be referred for specialist investigation and management of the AD and allergy.
  - As reflected by local growth charts, children with AD who exemplify failure to thrive at normal growth rates must be referred to specialists.

### **Special Patient Populations**

#### ***Specific Considerations for Children***

Treatment in the pediatric population should take into consideration factors related to the patient, disease, and treatment. It considers several factors such as a less experienced

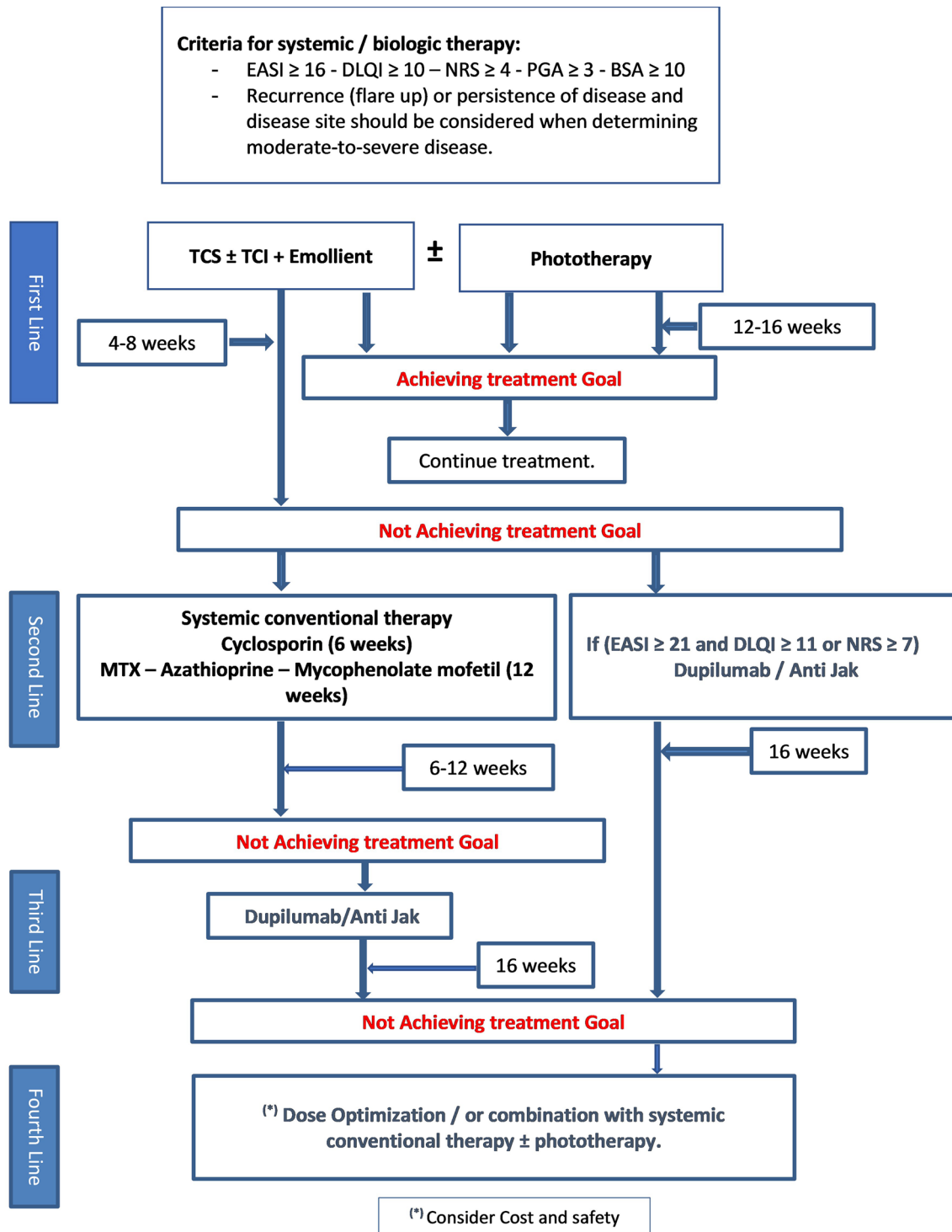


Fig. 2 Atopic dermatitis treatment algorithm

immune system, an incomplete skin barrier, and a larger surface area-to-body weight ratio,

which can result in an up to 2.7 times greater systemic exposure and risk of intoxication [7].

**Pharmacologic Therapies** The pharmacologic therapy for pediatrics is topical therapy using TCS, TCI, and/or PDE4 inhibitors (crisaborole). The principles of topical therapy are the same as in adults but are adapted with respect to increased immersion and altered surface-to-body weight ratio. Using less potent TCS (classes III and IV) in pediatrics is recommended, especially for sensitive areas such as the diaper area, face, and scalp. On the basis of safety data, TCIs are recommended as a steroid-sparing agent. They are approved for topical treatment for pediatric patients at least 2 years of age. It is also appropriate to use off-label TCIs in pediatric patients younger than 2 years of age [7, 13, 111, 112]. Crisaborole is indicated for topical treatment of mild-to-moderate AD in pediatric patients at least 3 months of age [80].

Phototherapy may be considered with precautions for children because of practical challenges, long-term concerns, and limited data on its use in pediatric AD [7]

Several systemic therapies are used to treat moderate-to-severe pediatric AD refractory to topical therapy and/or phototherapy. They include MTX, CsA, AZA, MMF, systemic corticosteroids (SCS), and dupilumab as the only biologic approved for use in patients 6 years or older.

We recommend physicians to be diligently cautious with regards to safety, tolerability, and allergenic profiles when treating children younger than 2 years of age. Systemic treatment should be introduced by qualified specialists only.

### ***Specific Considerations During Preconception, Pregnancy, and Lactation***

**Pharmacologic Therapies** The first-line pharmacologic therapy for AD during pregnancy and lactation are TCSs, as they are considered safe. Although prolonged use of high doses of higher-ranked topical steroids (300 g or more) has been reported to be associated with low birth weight in few cases, this is unlikely with appropriate use. Local side effects such as risk of striae may occur when using potent TCS on the abdomen and thighs [113].

Off-label use of TCIs (specifically tacrolimus) during pregnancy may be considered appropriate [113].

Phototherapy is considered a safe option for pregnancy. Supplementation of folic acid should be considered [113].

In moderate-to-severe AD during pregnancy which is refractory to topical therapy and/or phototherapy, the benefit of using systemic therapies must be considered in the light of patient characteristics and any potential or actual risk. Short-term SCS and CyA are considered relatively safe with close monitoring. Continuation of AZA treatment (halved dose) is considered possible on strict indication, while MTX and MMF are strictly contraindicated in pregnancy [7]. The decision to initiate systemic therapies for pregnant or lactating women should be taken in collaboration with obstetricians. Both male and female patients with AD who want to pursue a family life require special considerations to ensure treatment safety and efficacy.

### **Vaccination**

Common childhood immunizations in the first year are not associated with an increased risk of more severe AD or allergic sensitization [7]. Vaccinations, including the measles vaccine, are generally safe in hen's egg-allergic patients with AD [7]. Vaccinations against varicella are recommended to avoid severe cutaneous viral infections.

Parents of atopic children should be encouraged to fully vaccinate their children [7].

Currently, there is no evidence suggesting that AD is an independent risk factor for acquiring COVID-19 or suffering from a more severe course [114]. AD is not a contraindication to vaccination.

Because the vaccination response is mainly T helper cell 1 skewed, it is unclear if COVID-19 vaccination could cause worsening AD [114]. Systemic immunosuppressants and JAK inhibitors are used for AD treatment and may attenuate the vaccination response, but no attenuation was observed with dupilumab [114].

## CONCLUSION

General dermatologists and other healthcare providers frequently encounter AD in their patient populations. Optimal AD management requires thorough understanding of disease pathogenesis and treatment strategies. This document serves as a platform to enhance clinical practice parameters to meet every patient's treatment goals. Consequently, an individualized management plan should always be considered in order to provide best treatment for patients with AD.

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