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# Management of Children with Atopic Dermatitis: A Narrative Review

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## Abstract

**Context:** Atopic dermatitis is a chronic, relapsing skin disorder that affects all ages including infancy and childhood. There are many proved and unproved treatments for atopic dermatitis.
**Evidence Acquisition:** Data sources of this narrative review included studies about pediatric atopic dermatitis with the following keywords, pediatric, atopic dermatitis, immunity, acute, chronic, pruritic inflammatory skin disorder, infancy, childhood, diagnosis, management and treatment. All of the articles were written in English language with full text on management or treatment.
**Results:** Innate and adaptive immune system involved atopic dermatitis. Major characteristics of atopic dermatitis include pruritus, chronic or relapsing lesions and personal or family history of atopic disease. There is no specific treatment for atopic dermatitis. The treatment included rehydration, emollients, topical steroid, calcineurin inhibitors and immunosuppressant. Crisaborole topical ointment, a PDE4 anti-inflammatory topical agent (phase three of the research) could be effective in atopic dermatitis.
**Conclusions:** Avoidance from trigger factors and emollients are basic treatments of atopic dermatitis.

*Keywords:* Pediatrics, Dermatitis, Atopic, Theapy

## 1. Context

Atopic dermatitis (AD) is the most common chronic, relapsing and pruritic inflammatory skin disorder seen during infancy and childhood that has increased two to three times over the past three decades (1-3). It is characterized by an epidermal barrier abnormality, cutaneous inflammation, immune dysregulation with a systemic 'allergic' TH2 cell response, and frequent Staphylococcus aurous colonization (3). Atopic dermatitis involves approximately 10 to 30% of children (4). Ghaffari et al. (5, 6) showed that children atopic dermatitis prevalence is 5.98% and 6.52% in 6 to 7 and 13 to 14 year-olds in Iran, respectively. The diagnosis is usually made clinically after exclusion of other similar disorders. There are no laboratory specific tests for diagnosis of AD. The most important in the management of Ad is rehydration of the skin. Also avoidance of irritants and allergens is more important. Baths for a few minutes followed by immediate application of an emollient can improve skin manifestations (4). Occasionally, topical steroids or calcineurin inhibitors are used for relief of skin manifestations. Rarely, systemic immunosuppressants, such as steroid, are consumed in severe or refractory AD. The aim of this study was to review up to date papers about atopic dermatitis treatment in children.

## 2. Evidence Acquisition

Data sources of this narrative review included studies about pediatric atopic dermatitis indexed in several international databases and also a recent paper by one of the authors about prevalence of atopic dermatitis. Keywords for searching the databases included pediatric, atopic dermatitis, immunity, acute, chronic, pruritic inflammatory skin disorder, infancy, childhood, diagnosis and treatment. Studies that were not about children were excluded. Qualitative data are presented in this review. The inclusion criteria were as follows English language, full text, containing management or treatment. Also, we searched for all articles after 1990.

## 3. Results

Treatment of atopic dermatitis basically focuses on symptomatic relief. The association of the scientific medical societies in Germany (AWMF) guideline 013 - 027 on atopic dermatitis (neurodermitis) and the graded therapy modified from the current European atopic dermatitis guidelines provide a framework for a therapeutic approach, which must be modified depending on the patient's age, course, localization and emotional stress (Figure 1) (7).

| | |
|---|---|
| Stage 4<br>Persistent severe widespread dermatitis | •All measures required under stages 1,2, 3<br>•Systemic immunomodulatory therapy (for example, cyclosporine)<br>•Consider phototherapy (not in childhood; Caution! Not to be used with cyclosporine or azathioprine) |
| ↕ | |
| Stage 3<br>Moderate but at times severe widespread dermatitis | •All measures required under stages 1,2<br>•Higher-potency topical glucocorticosteroids at times in older children and adults<br>•Consider phototherapy (not in childhood) |
| ↕ | |
| Stage 2<br>Mild dermatitis | •All measures required under stage 1 PLUS<br>•Lower-potency topical glucocorticosteroids and or topical calcineurin inhibitors*<br>•Consider phototherapy (not in childhood)<br>•Consider adding topical antipruritic or antiseptic measures |
| ↕ | |
| Stage 1<br>Dry skin | •Basic skin care: hydration of skin, use of emollients<br>•Avoidance or reduction of trigger factors |

**Figure 1.** Current European Atopic Dermatitis Guidelines (8)

*3.1. General Care*

General measures for prevention and exacerbation of atopic dermatitis are as follows:

• Avoiding environmental aggravators such as chlorine, sand and grass, and washing immediately after coming in contact with these material;

• Wearing loose, cotton clothing and avoiding overheating;

• Performing soap-free washes;

• Taking short showers (two to three minutes is recommended);

Avoiding hot showers or baths; tepid water is luke-

warm, meaning that it is neither hot nor cold to the touch (2).

• Education about etiology, pathogenesis and current treatment could be effective in management of AD (9).

Also another study showed that a brief triple-P parenting intervention with education can lead to significant benefits in AD such as quality of life. Therefore, improving parental behavior could lead to improvement of childhood AD (10). Association of AD and behavioural difficulties could induce more severe AD and risk of low self-efficacy for management (11).

In another study, it was shown that patient education, as an adjunct to treatment, improves quality of life (QOL) and reduces disease severity. Support and education programs for parents can make an important contribution to treatment of AD (12).

• Aggravating factors and counseling for AD patients.

• Clothing: avoidance of skin contact with irritating fibres (wool, large fiber textiles); do not use tight and very warm clothing to avoid excessive sweating. New non-irritating clothing designed for AD children is currently being evaluated.

• Tobacco: avoid exposure.

• Cool temperature in the bedroom and avoidance of many bed covers.

• Increase emollient use with cold weather.

• Avoidance of exposure to herpes sores. Urgent visit if flare of unusual breakouts.

• Vaccines: normal schedule in non-involved skin, including egg-allergic patients.

• Sun exposure: no specific restriction with careful use. Usually helpful because of anti-inflammatory effect and improvement of epidermal barrier. Summer holidays in high altitude or at beach resorts are encouraged.

• Physical exercise, sports: no restriction. If sweating induces flares of AD, progressive adaptation to exercise. Shower and emollients after swimming pool.

• Cleansing and Rehydration

The most important step in management of AD is rehydration. Adequate rehydration preserves the stratum corneum barrier, reducing the direct effects of irritants and allergens and improving the effect of topically applied therapies. Therefore, decreasing the need for topical drugs such as steroids. Treatment choice of moisturizers for AD patients is largely influenced by personal preference. Lukewarm (not hot) soaking baths lasting 10 - 20 minutes are ideal (5, 13). The temperature of water should be warm (not hot) to prevent both vasodilation, which can trigger pruritus. Small amount of bath oils or emulsification agents may be used for older children and adolescents. Cleanser's pH should range from 5 to 6. The short duration of the bath (for 5 minutes) and the use of bath oils (two final minutes of bathing) can help rehydration. European experts have recommended bathing no more than three times weekly, especially in newborns (2, 14).

• Emollients

Baths should be followed by the immediate application of an emollient over the entire skin surface to retain moisture in the epidermis. Frequently recommended emollients are hydrophobic and ointment-based solutions, such as Vaseline petrolatum jelly and Eucerin.

Another type of moisturizing product is a ceramide-dominant, lipid-based emollient (TriCeram) aimed at repairing the stratum corneum barrier function lost in atopic dermatitis (15).

Wet dressings are very useful for chronically involved areas refractory to skin care and severe recalcitrant of atopic dermatitis (16). Only diluted corticosteroid preparations for occlusive dressings should be used to prevent hypothalamic-pituitary-adrenal axis suppression and local adverse effects on the skin. Wet wrap implementation should be delayed at least two to three days after beginning of antibiotic treatment for super infected lesions, to allow for observation of clinical improvement of infected sores (17).

Burow solution 1: 40 is a commonly used wet dressing because it is germicidal and directly suppresses weeping lesions by precipitation of protein.

Classification of moisturizers: these products are formulated in a variety of delivery systems including gels, oils, creams, ointments or lotions (Table 1).

In the management of eczema, lotions that contain a small amount of oil are less useful. Creams that predominantly contain water with an oil component are good for moisturising the skin that is not particularly dry or irritated. For the skin that is very dry, ointments consisting predominantly of oil mixed with a small amount of water are the most appropriate option (1, 18).

Non-steroidal, non-calcineurin inhibitors such as MAS063DP that contain glycyrrhetinic acid, Vitis vinifera extract and telmesteine in combination with shea butter (emollient) and hyaluronic acid (humectant) approved by food and drug administration (FDA) are used for relief of symptoms of AD. This is an effective mono-therapy for mild-to-moderate AD in pediatric patients (8).

### *3.1.2. Avoidance or Reduction of Trigger Factors*

#### *3.1.2.1. Food Allergy*

The correlation between AD and food allergies is about 30%. Food allergies are more common in children less than five years of age than older children. Milk, egg, wheat, soy, and peanut account for 75% of the food-induced exacerbation of AD. For diagnosis, there are a few allergy tests, includes; food-specific immunoglobulin E serum or skin

**Table 1.** Classification of Moisturizers (8)

| Class | Mode of Action | Biological Similarity | Some Examples |
|---|---|---|---|
| **Humectants** | Attract and bind water from deeper epidermis to SC | NMF in corneocytes | Glycerin |
| | | | Alpha hydroxy acids |
| | | | Hyaluronic acid |
| | | | Sorbitol urea |
| **Occlusive** | Forms hydrophobic film to retard TEWL of SC | Intercellular lipid bilayers | Carnauba wax |
| | | - Ceramide | Lanolin |
| | | - Cholesterol | Mineral oils |
| | | - Free fatty acids | Olive oil |
| | | | Petrolatum |
| | | | Silicone |
| **Emollients** | Smoothens skin by filling the cracks between desquamating corneocytes | Natural lipids found on skin and sebum | Collagen |
| | | | Colloidal oatmeal |
| | | | Elastin |
| | | | Glyceryl stearate |
| | | | Isopropyl palmitate |
| | | | Shea butter |
| | | | Stearic acid |

prick testing, prick to prick test and patch test. It is important to know that both tests have a high negative predictive value of greater than 95% and low positive predictive value of 40% to 60%. Skin test is suggested for children less than five years old. The best method for diagnosis of food allergy is the double-blind placebo-controlled food challenge test.

Therefore, clinical correlation and history are very important to help confirm the true presence of an allergy. A general elimination diet is not recommended and only indicated in case of a clinically relevant and documented food allergy.

In infants for reduction of AD, stepwise introduction of foods according to standard recommendations is required.

Otherwise a normal diet is administered, unless an allergy workup has proven the need to exclude a specific food.

*3.1.2.2. Aeroallergens*

Patients with AD have higher rates of sensitization to house dust mites, pollens, animal dander and fungi. Diagnosis of aeroallergens is skin test and serum specific IgE evaluation. Dust mite covers for pillows and mattresses can be used to decrease exposure, but evidence is limited supporting their overall effectiveness. Seasonal allergies can sometimes exacerbate AD; in these cases, the use of no sedating antihistamines can be helpful in conjunction with AD management (1).

- Indoor aeroallergens;
- House dust mites;
- Use of adequate ventilation of housing; keep the rooms well aerated even in winter;
- Avoid wall to wall carpeting;
- Remove dust with a wet sponge;
- Vacuum with an adequate filtered cleaner once a week; floors and upholstery;
- Avoid soft toys in bed (cradle), except washable ones;
- Wash bed sheets at a temperature higher than 55° every 10 days;
- Encase mattress and pillows in GoreTex or similar;
- Furred pets: avoid cats but not dogs, preventively. If allergy to furred pets is demonstrated, be firm on avoidance measures;
- Pollen: for sensitized individuals, close windows during peak pollen season on warm and dry weather and restrict stays outdoors. Aeration at night and early in the morning or by rainy weather. Avoid exposure to risk situations (lawn mowing). Place pollen filters in car. Clothes and pets can vectorize aeroallergens, including pollen.

*3.1.3. Phototherapy and Laser*

*3.1.3.1. Phototherapy*

Ultraviolet light may benefit some patients (4). Ultraviolet light in the UVB range may provide control and eliminate or markedly reduce the need for steroids. The new narrow band units are especially effective. Ultraviolet light in the UVA range has been used alone, in combination with oral psoralen administration (PUVA), or with high-dose UVA 1 (i.e., 340 - 400 nm spectrum units) (4). Generally, phototherapy reserved for refractory AD of traditional cares (moderate to severe). Of course, phototherapy is not

suitable for infants or young children but we can use it for older children and adolescents. However, long term NB-UVB therapy may induce skin cancer (21).

#### 3.1.3.2. Laser

Furthermore, 308-nm xenon chloride (XeCl) excimer laser could affect AD. In a study by Baltas E, it was shown that XeCl laser therapy is effective and well tolerated during 13 to 24 years with flexor surfaces involvement of AD (19).

In a systematic review, it was shown that the 308 XeCl could be considered for localized AD in adults and children. Also, this is more effective than clobetasol propionate in overcoming prurigo form of AD (20).

### 3.1.4. Topical Corticosteroids

Topical corticosteroids (TCSs) are the cornerstone of treatment for acute exacerbations of AD (Table 2). The choice of TCS is guided by location-applied severity of disease, extent of disease, availability, patient preference and cost.

Lower-potency TCSs are recommended for thin skin areas (e.g., face, neck, and genital area) and areas of occlusion (e.g., skin folds and intertriginous areas) where there is increased absorption of medication and higher risk of skin thinning. Higher-potency TCSs should be used on thick-skin areas (e.g., trunk and extremities) for a short time. Long term application of TCS is recommended twice-weekly. This use of intermittent TCS has been shown to be more effective than moisturizers alone (1, 4). Basically, low-to-mid potency TCS should be used as first-line treatment. No TCS is indicated for > 4 consecutive weeks of use (21).

In general, do not treat infants with topical steroids in the high-potency classes (class II or above). The proactive wet-wrap method with diluted corticosteroids has been advocated (22).

For children, the fingertip unit (FTU) has been shown to accurately measure an appropriate amount of medication. The FTU is defined as the amount of topical medication that will cover the child's index finger from the tip to the metacarpophalangeal joint. For topical steroids, 1 FTU covers the hand or groin, 2 FTUs cover the face or foot, 3 FTUs cover an arm, 6 FTUs cover a leg, and 14 FTUs cover the trunk.

The cutaneous side effects include purpura, telangiectasia, skin atrophy, striae, focal hypertrichosis, and acne and rosacea-like eruptions. Most cutaneous side effects are reversible after stopping TCS but may take months to resolve. Patients can also develop an allergic contact dermatitis or type 4 hypersensitivity reactions to TCS themselves or to the ingredients within the formulation.

Systemic side effects with TCS use, such as hypothalamic-pituitary-adrenal (HPA) suppression, are extremely low. The risk of HPA suppression increases in children, who have a high body surface area to weight ratio, individuals receiving other forms of corticosteroids (e.g., inhaled, oral and intranasal), and with prolonged and continued use of high-potency TCS. Other systemic side effects, such as hyperglycemia and hypertension, have been rarely reported. The risk of development of cataracts and glaucoma with TCS use has not been fully established. Adrenal suppression is greatest in infants and young children with severe AD with use of more potent and extensive therapy.

Hydrocortisone 17-butyrate 21-propionate (HBP) is a medium potent, non-halogenated double-ester of hydrocortisone (0.1% cream or ointment). This drug was shown to have a good efficacy on oozing and a lichenified eczematous skin disease including AD. This is safe and effective for very young children (23).

A recent study showed that to enhance the local topical activity of Hydrocortisone (HC), the terminal inactive metabolite of prednisolone, $\Delta$1-Cortienic Acid ($\Delta$1-CA), is added to HC, as $\Delta$1-CA preferentially binds transcortin, liberating more HC to elicit its therapeutic effect (24).

There are variable reasons for failure of management of atopic dermatitis (Figure 2).

### 3.1.5. Topical Calcineurin Inhibitors

Topical calcineurin inhibitors (TCIs) are steroid-sparing agents that can be used in conjunction with TCS or by themselves. They are derived from Streptomyces bacteria and inhibit T-cell activation, thereby blocking proinflammatory cytokines and mast cell activation. The various formulations of TCI are listed in Table 3. Topical Calcineurin Inhibitors do not have the cutaneous adverse side effects that TCS have. Their use is indicated when there is evidence of steroid induced atrophy, in areas at high risk for skin thinning, and when TCSs have been used continuously in the long-term (4). Like TCSs, TCIs can also be used as a maintenance therapy, one to three times per week to prevent flares at recurrent sites of disease. Side effects of TCI include local reactions of burning and stinging.

Although systemic use of TCI may induce malignancy, but at present, there is no increased risk of malignancy with topical TCIs in the recent studies. Therefore, the long-term use of topical TCIs is safe (21).

Physicians are advised to use the following guidelines when prescribing topical TCIs (25, 26):

• Short term use or intermittently as needed, it is better if not used daily for a long time.

**Table 2.** Topical Corticosteroids Formulations by Class (1)

| Class | Medication | Strength (%) | Form |
|---|---|---|---|
| **I. Super potent** | Augmented betamethasone dipropionate | 0.05 | Ointment |
| | Clobetasol propionate | 0.05 | Ointment, cream, solution, foam |
| | Diflorasone diacetate | 0.05 | Ointment |
| | Fluocinonide | 0.1 | Cream |
| | Halobetasol propionate | 0.05 | Ointment, cream |
| **II. High potency** | Betamethasone dipropionate | 0.05 | Ointment, cream, foam, solution |
| | Budesonide | 0.025 | Cream |
| | Desoximetasone | 0.25 | Ointment, cream |
| | Diflorasone diacetate | 0.05 | Cream |
| | Fluocinonide | 0.05 | Ointment, cream, gel |
| | Halcinonide | 0.1 | Ointment, cream |
| | Mometasone furoate | 0.1 | Ointment |
| | Triamcinolone acetonide | 0.5 | Ointment, cream |
| **III–IV. Medium potency** | Betamethasone valerate | 0.1 | Ointment, foam |
| | Clocortolone pivalate | 0.1 | Cream |
| | Desoximetasone | 0.05 | Cream |
| | Fluocinolone acetonide | 0.025 | Ointment, cream |
| | Flurandrenolide | 0.05 | Cream |
| | Fluticasone propionate | 0.005 | Ointment |
| | Mometasone furoate | 0.1 | Cream |
| | Triamcinolone acetonide | 0.1 | Ointment, cream |
| **V. Lower medium potency** | Hydrocortisone butyrate | 0.1 | Ointment, cream, solution |
| | Hydrocortisone probutate | 0.1 | Cream |
| | Hydrocortisone valerate | 0.2 | Ointment, cream |
| | Triamcinolone acetonide | 0.25 | Ointment, cream |
| **VI. Low potency** | Alclometasone | 0.05 | Ointment, cream |
| | dipropionate | 0.05 | Ointment, cream |
| | Desonide | 0.01 | Cream, oil, solution |
| | Fluocinolone acetonide | 0.025 | Cream |
| | Flurandrenolide | | |
| **VII. Lowest potency** | Dexamethasone | 0.1 | Cream |
| | Hydrocortisone | 2.5 | Ointment, cream, lotion |
| | Hydrocortisone acetate (over the counter) | 0.5 and 1.0 | Cream, ointment |

**Table 3.** Topical Corticosteroids (1)

| Medication | Pimecrolimus (Elidel) 1% | Tacrolimus 0.03% | Tacrolimus 0.1% |
|---|---|---|---|
| **Vehicle** | Cream | Ointment | Ointment |
| **FDA approved** | Mild to moderate AD | Moderate and severe AD | Moderate and severe AD |
| | > 2 y of age | > 2 y of age | > 15 y of age |
| **TCS equivalent** | No direct comparison study done; thought to be low-mid potency | Low–mid potency | Mid potency |

Abbreviation: FDA, food and drug administration.

• Avoid use in immunocompromised patients or in those with neoplasms.

• Encourage sun protection to reduce the risk of photo carcinogenesis.

In a recent study, it was shown that calcineurin inhibitors and corticosteroids have similar efficacy for atopic dermatitis. Calcineurin inhibitors are associated with higher costs and adverse events, such as skin burning and pruritus. Calcineurin inhibitors remain suitable as adjunctive therapy to be used with topical steroids for atopic dermatitis (27).

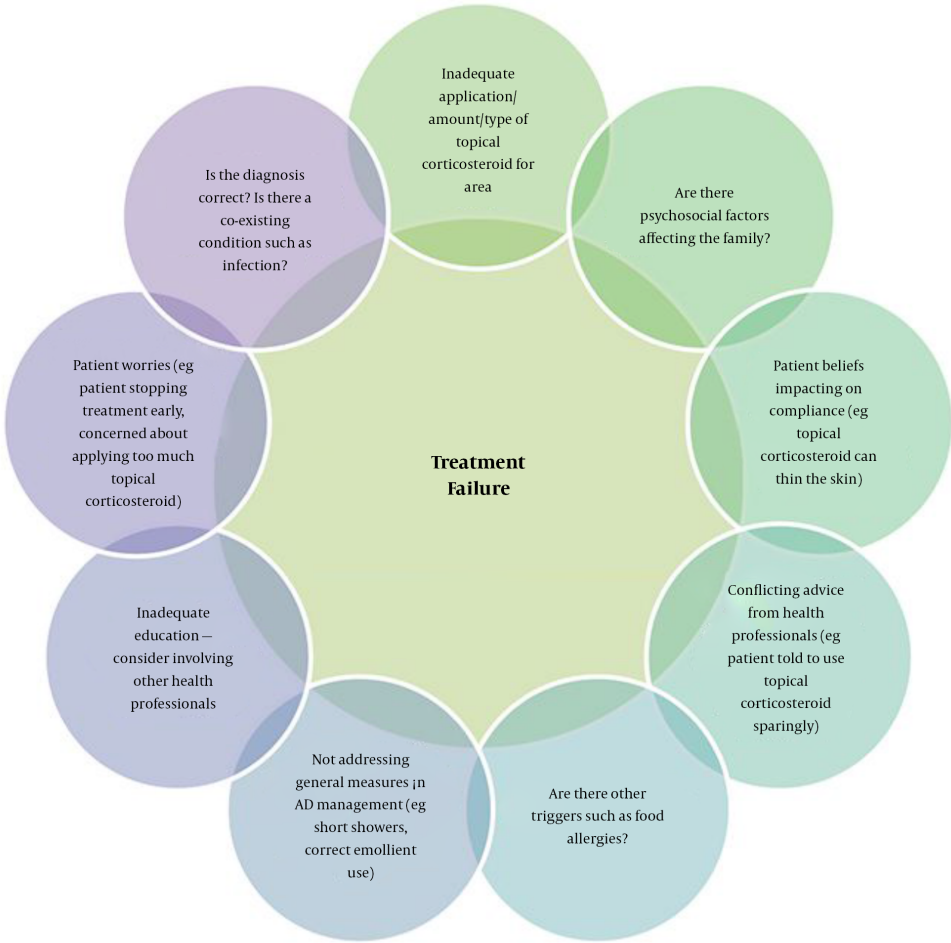


**Figure 2.** Common Causes of Treatment Failure With Topical Corticosteroids (6)

*3.1.6. Coal Tar*

Coal tar may restore filaggrin expression and the Th2-mediated down-regulation of skin barrier proteins by aryl hydrocarbon receptor (AHR) activation and STAT6 dephosphorylation, thus diminishing spongiosis, apoptosis, and CCL26 expression in AD lesions. Tar preparations may be considered in selected cases, e.g. those with lichenification. The use of coal tar in infants is controversial (14).

*3.1.7. Emerging Topical Therapies*

Crisaborole topical ointment, 2%, a PDE4 anti-inflammatory topical agent (phase 3 of research) could be effective in AD (28). Other PDE4 anti-inflammatory topical agents such as DRM02 (Dermira, Menlo Park, CA) and LEO 29102 (LEO Pharma, Ballerup, Denmark) have been identified as a treatment for AD. Non-PDE4 inhibitor topical agents in development include GSK2894512 (GlaxoSmithKline, Brentford, Middlesex, UK), a non-steroidal anti-inflammatory that has been investigated (29). Two large, randomized, controlled, phase 3, pivotal clinical trials assessing the efficacy and safety of crisaborole topical ointment, 2% in children, adolescents, and adults with mild to moderate AD were recently completed with positive results (30). In another study, it was shown that crisaborole could be effective in management of acute or chronic AD, especially mild to moderate AD in children (2).

In a phase 2 study, OPA-15406, a phosphodiesterase-4 inhibitor, in patients 10 to 70 years of age was suggested to provide an effective therapeutic modality for patients with mild to moderate AD (28).

*3.1.8. Systemic Immunosuppressant*

The most commonly used systemic immune-modulating medications used for AD are azathioprine,

cyclosporine, mycophenolate mofetil and methotrexate. These medications have been recommended for the treatment of refractory AD when optimal topical treatments and/or phototherapy has been ineffective (18). Cyclosporine, methotrexate, mycophenolate mofetil (MMF) and azathioprine are not FDA approved for the treatment of atopic dermatitis (31).

#### 3.1.9. Management of Pruritus

Antihistamines are widely used as a therapeutic adjunct in patients with atopic dermatitis to treat both pruritus and eye irritation (32). The sedating antihistamines appear to be most effective (e.g., diphenhydramine, hydroxyzine, and cyproheptadine).

Antihistamines may be tried to decrease pruritus and permit sleep during flares, but may affect sleep quality. Long-term use in children is not recommended. Ongoing studies concentrate on the blockade of alternative histamine receptors such as H4R, which may be more important in AD (14). No sedating preparations such as fexofenadine, cetirizine, or loratadine may occasionally also be useful, especially when there is an urticarial component or concurrent allergic rhino conjunctivitis (33).

Several studies have demonstrated that leukotriene receptor antagonists (LTRAs) are effective in the treatment of atopic dermatitis (34). Doxepin, a tricyclic antidepressant with potent H1 and H2 blocking properties, may be used as a second-line treatment if others fail (4, 35). Topical calcineurin inhibitors appear to be effective in controlling pruritus (36-38).

If there is widespread infected atopic dermatitis, short courses of oral antibiotics are recommended but there is no evidence that topical or long-term use of antibiotics is helpful in preventing atopic dermatitis.

### 3.2. Infections

Staphylococcus aureus is a frequent skin colonizer in patients with atopic dermatitis, isolated from the skin lesions of 76 to 100% of patients. Topical Mupirocin is suggested for local infection and oral antibiotics for extensive infection (39). Obtaining swabs from affected skin and nares may be helpful to identify infection and obtain direct further management (18).

Dermatophyte infections are more common in AD and can be treated with local or systemic anti-fungal drugs (40).

Eczema herpeticum or Kaposi's varicelliform eruption should be treated immediately with oral antiviral therapy. Also, widespread molluscum contagiosum infections may develop in AD (41).

#### 3.2.1. Unproven Therapies

##### 3.2.1.1. Allergen Immunotherapy

Specific immunotherapy (SIT) in Limited studies have shown clinical improvement in mild to moderate AD cases, but no effect on more severe patients. The summary of the data at present does not warrant the use of SIT in children with AD. Using sub-lingual immunotherapy in AD is under study and more evidence is needed to support its clinical use (42). However, in another study, SIT (especially subcutaneous immunotherapy), was considered for selected patients with house dust mite, birch or grass pollen sensitization, who had severe AD, a positive corresponding atopy patch test and didn't show a good response to conventional treatments. More studies are needed to confirm IT for AD (14).

##### 3.2.1.2. Substances Including Interferon Gamma, Omalizumab, Probiotics

Chinese herbal medications and vitamin D may be used in a refractory AD (4, 43).

##### 3.2.1.3. In Phase I and II Studies of Adults With Moderate-to-Severe AD, Dupilumab (IL-4 Receptor $\alpha$ Subunit) Significant Improvements in Clinical Efficacy and Further Support the Application of Th2 Cytokine Antagonists in the Treatment of This Disease

There is no study on children (44).

##### 3.2.1.4. Traditional Chinese Medicine (TCM), especially Chinese Herbal Medicine (CHM)

Traditional Chinese medicine (TCM), especially Chinese herbal medicine (CHM), is used commonly in allergic disorders such as AD, but there is no significant data for routine treatment of CHM in atopic dermatitis (45).

In vitro study, Huang-Lian-Jie-Du Decoction (HLJDD), a well-known Chinese herbal formula exerted significant anti-inflammatory and anti-allergic effects suppressive via the NF-$\kappa$B and MAPKs inactivation and I$\kappa$B$\alpha$ degradation in the LPS-stimulated RAW24.7 cells, and inactivation of MAPKs and Lyn pathway in antigen-induced RBL-2H3 cells. In vivo study of HLJD is currently in progress in the same laboratories. Therefore, we need other studies to support the use of HLJDE for the clinical treatment of AD (46).

##### 3.2.1.5. Some Supplements, Including Vitamins, Fish Oil, and Plant-Derived Essential Fatty Acids Do Not Appear to Be Beneficial for the Treatment of AD

There is controversy for vitamin D supplement in treatment of AD. Topical vitamin D may worsen AD (47-49).

In a recent study, it was shown that low dose of vitamin E (400 IU/day) can be effective in the treatment of AD patients (aged 10 to 50 years). Of course, we need other studies to confirm this (50).

One study suggested that IVIG therapy could be effective and safe for children with resistant atopic dermatitis (51).

Autogenously adipose-derived mesenchyme stem cells (AD-MSCs) did not significantly reduce the clinical signs and symptoms of canine atopic dermatitis. Also, human umbilical cord blood-derived MSCs (hUCB-MSCs) might be effective in adults with moderate-to-severe AD. However, there is no study on the effect of MSCs on children with AD (52, 53).

Seeking psychological counseling, biofeedback, relaxation techniques, massage therapy, and behavioral modifications, if emotional stressors are a contributing factor to atopic dermatitis, is necessary.

### *3.2.2. Prevention*

Breast feeding, especially exclusive breastfeeding for the first six months of life, hypo allergic hydrolyzed formula, probiotics and prebiotics, may reduce the incidence or severity of AD (4). Another study showed no preventive effect of exclusive breastfeeding on AD (54, 55).

However, whether breastfeeding, hydrolyzed formula and probiotics could help prevent development of atopic dermatitis in children is not clear and needs more studies.

### *3.2.3. Prognosis*

Spontaneous resolution will occur in 40% - 60% of AD after five years of age, especially for a mild form. Twenty percent achieve total resolution and 65% reach partial resolution (less severe) when adolescent. After resolution during childhood, more than 50% relapse in adulthood. Predictive factors of poor prognosis for Ad are widespread AD in childhood, filaggrin gene null mutations, concomitant allergic rhinitis and asthma, family history of Ad in parents and siblings, early age at onset of AD, being an only child and very high serum IgE levels (4).

## 4. Conclusions

Avoidance from irritants and allergens is associated emollients and antihistamines are basically the treatment of AD in the children. In smaller group that refractory or moderate to severe AD use second or third line of therapy such as anti-leukotriene, laser, phototherapy and immunosuppresses.

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