

Treatment of Eczema: Corticosteroids and Beyond

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Abstract Atopic dermatitis (AD) is a chronic inflammatory skin condition that requires a manifold approach to therapy. The goal of therapy is to restore the function of the epidermal barrier and to reduce skin inflammation. This can be achieved with skin moisturization and topical anti-inflammatory agents, such as topical corticosteroids and calcineurin inhibitors. Furthermore, proactive therapy with twice weekly use of both topical corticosteroids and calcineurin inhibitors in previously affected areas has been found to reduce the time to the next eczematous flare. Adjunctive treatment options include wet wrap therapy, anti-histamines, and vitamin D supplementation. Bacterial colonization, in particular *Staphylococcus aureus*, can contribute to eczematous flares and overt infection. Use of systemic antibiotics in infected lesions is warranted; however, empiric antibiotics use in uninfected lesions is controversial. Local antiseptic measures (i.e., bleach baths) and topical antimicrobial therapies can be considered in patients with high bacterial colonization. Difficult-to-treat AD is a complex clinical problem that may require re-evaluation of the initial diagnosis of AD, especially if the onset of disease occurs in adulthood. It may also necessitate evaluation for contact, food, and inhaled allergens that may exacerbate the underlying AD. There are a host of systemic therapies that have been successful in patients with difficult-to-treat AD, however, these agents are limited by their side effect profiles. Lastly, with further insight into the pathophysiology of AD, new biological agents have been investigated with promising results.

Keywords Atopic dermatitis · Topical calcineurin inhibitors · Topical corticosteroids · Difficult-to-treat atopic dermatitis · Contact dermatitis

Introduction

Atopic dermatitis (AD) was first described as a distinct clinical entity in the 1930s where treatment focused on the use of topical remedies like emollients [1]. The development of topical hydrocortisone in the early 1950s led to a significant impact not only in the treatment of AD but also in the understanding of the immunologic mechanisms [2, 3]. The discovery of a predominating Th2-cytokine profile and defects in the epidermal barrier (i.e., filaggrin mutations) in AD skin paved the way for the development of more effective therapeutic agents. However, despite these therapeutic advances seen so far, AD still affects approximately 30 % of children and 3 % of adults [4]. This article will focus on the current guidelines for AD management which includes topical and systemic therapies as well as modification of environmental exposures. A review of current developments in potential immunomodulatory agents will also be discussed.

Epidermal Barrier-Restoring Therapies

Moisturizers

Atopic skin has lower water and lipid content which makes it drier than healthy skin and favors the formation of cracks in the epidermis [5, 6]. This facilitates the entry of allergens and microbes which can elicit an immune response and further irritate the skin. Moisturizers are the cornerstone in AD treatment as they improve the epidermal barrier by hydrating the

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skin and sealing it to retain moisture [7]. There are a wide variety of moisturizers available on the market (i.e., ceramide-rich preparations, petrolatum); however, there is limited data to recommend one type over another [8]. Patients and their families should thus be given several moisturizer options to ensure that they are compliant with the moisturization regimen [7]. The importance of daily moisturization to reduce the severity of AD and the need for steroids should also be stressed to patients and their caregivers [9–11]. A recommended regimen includes warm baths for at least 10 min followed by the application of the moisturizer within 3 min onto damp skin to trap moisture [8].

Topical Corticosteroids

Topical corticosteroids (TCs) are effective medications for the treatment of AD when used concurrently with an optimal skin moisturization regimen. The potency of TCs is related to saturation of the glucocorticoid receptors in different cell types and is reflected in vasoconstrictor assays. In the USA, TCs are classified from class 1 to 7; class 1 is the most potent whereas class 7 is the least potent. An alternate classification system categorizes TCs into super-, high-, moderate-, and low-potency strengths. High- and intermediate-potency TCs are warranted for acute eczema flares and lichenified lesions for a short period of time. Once AD is controlled, treatment can then be transitioned to low-potency TCs as maintenance therapy. “Proactive treatment” with twice weekly application of TCs to previously affected areas also increases the time interval to the next flare [12].

Although effective in AD, TCs are associated with both topical and systemic side effects. The cutaneous side effects include skin atrophy, telangiectasia, striae, hypopigmentation, and perioral dermatitis. The eyelids, face, intertriginous areas, and genitalia have increased potential for transepidermal corticosteroid penetration thus potent fluorinated TCs should be avoided in these areas. Systemic side effects of TCs, though rare, include suppression of the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis suppression depends on several factors including the potency of the TCs, the site of application, the occlusiveness of the preparation, the involved body surface area, and the duration of therapy. Young children and infants are also at greater risk for these side effects [13, 14]. Results from studies with TC preparations, such as fluticasone propionate and mometasone furoate, revealed that once daily dosing led to less systemic absorption and was comparable in efficacy to twice daily dosing [15, 16]. Reduced frequency of TCs not only improves compliance but also reduces the potential for side effects.

Contact allergy to TCs can complicate the management of AD and has been reported in 0.5–5.8 % of allergic contact dermatitis (ACD) patients [17]. The cross-reactivity of TCs is based on two immune recognition sites—C6/9 and C16/

17 substitutions—and is classified as groups A, B, C, D-1, and D-2. Sensitization can occur through skin, airborne, oral, and parenteral routes [18]. Patients with impaired skin barrier [19] such as refractory eczema, AD, chronic venous leg ulcers, stasis dermatitis, and multiple medicament sensitivities are at increased risk of corticosteroid ACD. Contact sensitivity to TCs should be suspected in the following scenarios: worsening or persistent dermatitis despite adequate TCs therapy, initial improvement with TCs followed by worsening of symptoms, and changing clinical pattern of disease after TCs use.

Patch testing (PT) to corticosteroids is complicated by the inherent, anti-inflammatory nature of the medication itself. False-negative results can occur if testing is done at too high or too low of a concentration. Also, delayed patch test readings should be done 7–10 days following application since about 30 % of ACD to TCs are missed by conventional readings [20]. Patch test materials for amcinonide, betamethasone-17, 21-dipropionate, betamethasone-17-valerate, budesonide, clobetasol-17-propionate, desoximetasone, dexamethasone, hydrocortisone, hydrocortisone 17-butyrate prednisolone, tixocortol-21-pivalate, and triamcinolone acetonide are commercially available. The patient’s own commercial steroid [18], along with the vehicle and preservatives contained in the preparation, should also be tested. Coopman, et al. [21] suggested that there is considerable cross-reactivity not only within but also between the four major groups of TCs preparations. Ninety percent of ACD to corticosteroids can be detected with PT to tixocortol pivalate, budesonide, triamcinolone and the patient’s own commercial steroid [22]. Although rare, patients sensitized to TCs can develop a systemic contact dermatitis with administration of the corticosteroids through an oral, parenteral, intramuscular or inhalational route [23]. Once an allergy to TCs has been confirmed through PT, avoidance of all TCs within that group is recommended due to the potential for cross-reactivity (Table 1).

Topical Calcineurin Inhibitors

Calcineurin is a calcium-dependent phosphatase that dephosphorylates transcription factor nuclear factor of activated T cells (NFAT) which is responsible for the transcription of various cytokines. Calcineurin inhibitors block cytokine production in T cells, keratinocytes, and Langerhans cells whose effector functions contribute to the pathogenesis of AD [24–26].

Topical calcineurin inhibitors (TCIs) are FDA-approved for short-term and intermittent long-term use in moderate to severe AD in children (>2 years old) and adults [8]. In the USA, TCIs are available as ointments (tacrolimus 0.03, 0.1 %) and creams (Pimecrolimus 0.1 %). Tacrolimus 0.03 % ointment is the only TCI approved for children aged 2–15 years old. Tacrolimus 0.1 % ointment is comparable in efficacy to mid-potency TCs but, unlike TCs,

Table 1 Structural groups of corticosteroids: cross-reactivity based on two immune recognition sites—C 6/9 and C16/17 substitutions

Topical corticosteroids	Systemic corticosteroids
Group A: hydrocortisone and tixocortol pivalate C17 or C21 short chain ester Prevalence of positive PT=2.7 % Patch Test Substance: Tixocortol 21-pivalate Cross reacts with Group D2	
Cloprednol [Syntestan® (Germany)] Dichlorisone Acetate [Dermaren® (Spain)]	Cortisone acetate Hydrocortisone-21-acetate
Fluorometholone [FML® Ophthalmic O] Fluprednisolone acetate [Medinost® (Georgia)] [Prednisolon STADA® (Germany)]	Methylprednisolone acetate [Depo Medrol®] Prednisone
Hydrocortisone [Hytone® C/L (1/2.5 %), Class 7] [Cortaid®, C/O/spray, (Class 7)] [Egocort® C 1 %, (Class 7)]	Prednisolone acetate
Medrysone [HMS® 1.0 %] [LIQUIFILM® sterile ophthalmic suspension] Meprednisone [Cortipyrén®, (Argentina)] [Deltisona B®, (Argentina)] [Meprednisone All Pro®, (Argentina)]	Hydrocortisone sodium [Solu-cortef] Methylprednisolone acetate intra-articular, intralesional, intrasynovial
Prednisolone acetate [Pred Forte® eye drops]	Fludrocortisone acetate Tablets
Tixocortol [Pivalone®, Tunisia; Congo; France; Romania; Vietnam] [Thiovalone® (Tunisia, France)]	
Group B: Acetonides C16, C17 cis-ketal or -diol additions Prevalence of positive PT=1.6 % Patch Test Substance: Budesonide, Triamcinolone acetonide Budesonide specifically cross reacts with Group D2	
Amcinonide [Cyclocort® (0.05 %), Class 2]	Triamcinalone
Budesonide (Pulmicort®, Butacort®, Entocort®)	Triamcinalone benetonide
Desonide [Tridesilon®, DesOwen® O (0.05 %), Class 5] [DesOwen® (0.05 % C/L), Class 6]	Triamcinalone diacetate
Fluocinolone acetonide [Synalar®, Synemol® (0.01–0.2 %), Class 4] [Synalar®, Synemol® C (0.025 %), Class 5] [Capex® shampoo, Dermasmooth®/FS oil (0.01 %), Class 6]	Triamcinalonehexacetone
Fluocinonide [Lidex® C/G/O (0.05 %), Class 2] [Vanos® C (0.1 %), Class 1] Flunisolide [Aerospan® Inhaler] Halcinonide [Halog® C/O (0.05 %), Class 2]	

Table 1 (continued)

Topical corticosteroids	Systemic corticosteroids
Triamcinalone acetonide [Kenalog®, Aristocort® C (0.5 %), Class 3] [Kenalog®, Aristocort A® O (0.1 %), Class 4] [Aristocort A® C, Kenalog® L (0.025 %), Class 6]	
Group C: non-esterified Betamethasone C16 methyl group Prevalence of positive PT=<0.2 %	
Desoximetasone [Topicort® C/O (0.25 %), Class 2] [Topicort LP® C/O (0.05 %), Class 4]	Betamethasone sodium phosphate Injectable Suspension
Difluocortolone (pivalate, valerate) [Nerisone C® C/O (Difluocortolone valerate) (Foreign)]	Dexamethasone acetate
Flumethasone (foreign, vet use)	Paramethasone acetate
Fluocortin butyl [Vaspit®, Spain]	Dexamethasone-sodium phosphate Injection
Fluocortolone (hexanoate, pivalate, caproate) [Ultraproct®] Fluprednidene acetate	
Halometasone [Halometasone 0.05 %, Class 3]	
Group D 1 C16 methyl group & halogenated B ring Prevalence of positive PT=0.8 % Patch Test Substance: Clobetasole-17-propionate	
Aclometasone dipropionate [Aclovate® C/O (0.05 %), Class 6]	Beclomethasone dipropionate
Betamethasone 17 valerate [Luxiq® F (0.12 %), Class 3]	Betamethasone dipropionate
Betamethasone dipropionate [Diprolene® O (0.05 %), Class 1] [Diprolene® C AF (0.05 %), Class 2] [Diprosone® (0.05 %), Class 3]	
Clobetasol propionate [Clobex® L/spray/shampoo, Dermovate® C/O, Olux® F, Temovate® C/O/S (0.05 %), Class 1]	
Clobetasone 17 butyrate [Eumovate®, Class 1]	
Diflorasone Diacetate [ApexiCon®, Psorcon® C/O, Florone® O (0.05 %), Class 1]	
Fluticasone propionate [Cutivate® O (0.005 %), Class 3] [Cutivate® C (0.05 %), Class 5]	
Halobetasol [Ultravate® C/O (0.05 %), Class 1]	
Mometasone Furoate [Elocon® O (0.1 %), Class 3] [Elocon® C/L (0.1 %), Class 4]	
Group D2: Labile esters w/o C16 methyl nor B ring halogen substitution Prevalence of positive PT=0.8 % Cross reacts with Group A and Budesonide Patch Test Substance: Hydrocortisone-17-butyrate Hydrocortisone 17-butyrate	

Table 1 (continued)

Topical corticosteroids	Systemic corticosteroids
[Locoid® C/L/O (0.1 %), Class 4] Hydrocortisone-17-valerate [Westcort® O (0.2 %), Class 4] [Westcort® C (0.2 %), Class 5] Prednicarbate [DermAtop® C (0.1 %), Class 5] Methylprednisolone aceponate [Advantan C/O, Mid-potency (Foreign)]	

In parenthesis are examples of products available in different countries with their potency classification. For this manuscript, the allergenicity is classified as groups A, B, C, D1, and D2 and the potency is from classes 1–7; 1 being the most potent and 7 being the least potent. The potency classification and the source country (found in the USA if not indicated) are identified when available. Also, classification of potency may vary depending on different factors such as the vehicle and reference source
C cream, G gel, O ointment, L lotion, F foam, S solution

prolonged use of TCIs do not cause skin atrophy [27]. Thus, TCIs are preferred over TCs for moderate dermatitis of the face and eyelids [8].

AD management includes a “proactive” treatment approach to prevent AD flares because subclinical inflammation still persists in quiescent lesions [7, 28]. Clinical trials with TCs and TCIs as proactive therapy have demonstrated overall AD improvement with reduced flares, improved quality of life, and lower treatment costs [28–30]. However, it is unclear which agent is more superior in terms of safety and clinical efficacy. A randomized controlled study compared tacrolimus 0.1 % ointment with betamethasone valerate 0.1 % cream as maintenance therapy (4 weeks) in 20 patients with well-controlled AD [31]. Because of its more potent anti-inflammatory effect, betamethasone also reduced the function and integrity of the skin barrier in quiescent AD, making it comparable to skin with active disease. Contrastingly, tacrolimus preserved skin barrier integrity and function to levels comparable with healthy skin. The investigators stated that results were likely independent of a base effect (tacrolimus ointment vs. betamethasone cream) as the negative effects seen with betamethasone cream were greater than previously reported differences between ointment and cream bases. Other studies further support the observation that TCIs preserve the integrity of the epidermis better than TCs [32, 33]. Although these results suggest that TCIs fare better as maintenance therapy, more studies are required to confirm this observation.

Side effects of TCIs include a localized, burning sensation that diminishes with continued use (approximately 3 days of use) and an increased susceptibility to viral infections (i.e., herpes simplex virus) [8]. In 2006, the FDA issued a black box warning for risk of malignancy based on seven pediatric cases [34]. The indication for TCIs were revised to *second-line* therapy for children (>2 years old) and adults with AD.

Although the risk of malignancy with oral calcineurin inhibitors is well known, TCIs have low systemic absorption [34]. TCIs do, however, infiltrate inflamed and TC-treated skin to a deeper extent than healthy skin; tacrolimus ointment exhibited the greatest infiltration [35, 36]. This exposure will decrease as skin barrier function is restored through the effects of the TCIs itself.

Serum levels of tacrolimus 0.1 % and pimecrolimus cream were compared in 37 adult patients with moderate to severe AD [37]. TCIs were used for 13 days total and serum drug levels were measured on days 1, 5, and 13. The highest serum concentrations for topical pimecrolimus and tacrolimus were 1.51 and 2.39 ng/mL, respectively, which are well below the target concentration for systemic calcineurin inhibitors (5–20 ng/mL). In infants, serum concentration with topical pimecrolimus cream ranged from 1.8 to 4.14 ng/mL, likely due to a greater body surface area to weight ratio [34].

Multiple retrospective studies, including a case–control study of 293,253 AD patients, did not reveal an increased risk of lymphoma with TCIs [38, 39]. These results, however, were limited due to poor study design and short study duration. A long-term study (10 years) with 625,915 patients revealed a dose-dependent risk of T cell lymphoma with topical tacrolimus [40]. The incidence rate of lymphoma in AD patients was as follows: 8.55 per 10,000 for topical tacrolimus; 5.06 per 10,000 for pimecrolimus; 6.29 per 10,000 for TCs; and 7.83 per 10,000 for non-users. The accuracy of this data was limited by large confidence intervals. Other factors may also contribute to these observations such as an independent risk of lymphoma in severe AD [34].

Due to the lack of prospective studies, many physicians and patients are hesitant to use TCIs and opt for TCs instead, which also have serious side effects. Two ongoing 10-year prospective trials with two registries (A Prospective Pediatric Longitudinal Evaluation to Assess the Long-Term Safety, APPLES; Pediatric Eczema Elective Registry, PEER S) are evaluating the risk of malignancy with TCIs in pediatric patients in hopes of providing more insight into this dilemma [34]. Preliminary results from the APPLES trial have revealed no reports of adverse events or malignancy in 1000 AD children (mean age 4.8 years old) with exposure to tacrolimus ointment for a mean duration of 2.5 years [41]. Similarly, the PEERS trial has found no “safety findings” to date in AD children with exposure to pimecrolimus cream [42].

Wet Wraps

Wet wrap therapy (WWT) was first described in 1987 and has been demonstrated to be an effective treatment option in moderate to severe AD [43]. It involves a soaking bath followed by the application of topical emollients or medications (typically TCs although TCIs can be used as an off-label use), [44] onto eczematous lesions. These lesions are then “wrapped” by a

“wet” layer of dressing (i.e., pajamas, ACE bandages, tube socks, etc.) that has been soaked in warm water and wringed. A “dry” layer of dressing is then placed over the wet layer for approximately 8 h or while the patient is sleeping. The dressings can then be removed in the morning. Occlusion of skin with dry dressings alone has not shown any benefit over conventional open therapy [45]. Furthermore, a randomized controlled trial with 39 children demonstrated that WWT combined with TCs fared better than with emollients alone [46]. Patients who used TCs experienced a faster and more dramatic improvement of symptoms.

WWT provides a moist environment that increases skin hydration and absorption of topical medications, helping to restore the damaged epidermal barrier [47]. WWT also helps to disrupt the itch-scratch cycle by creating a skin barrier. The effectiveness of WWT has been demonstrated by several studies [48–54]; however, a recent study evaluated WWT under direct supervision and, unlike previous studies, included a follow-up assessment [55]. Investigators noted a significant improvement in disease severity, measured by scoring atopic dermatitis (SCORAD) scores, which lasted up to 1 month after WWT discontinuation.

With increased absorption of topical medications, there is concern for systemic absorption of corticosteroids especially in children. A study of 12 children with moderate to severe AD who underwent WWT with different dilutions (5, 10, 25, 50 %) of fluticasone propionate (FP) 0.05 % cream was found to have significant symptom improvement, independent of the potency of FP [54]. Suppression of the HPA axis was observed in children using higher potencies of FP. Findings from this study suggest that lower potency TCs do not affect the effectiveness of WWT and decreases the risk of HPA axis suppression.

An important aspect of WWT is education on the proper application technique. WWT can lead to skin maceration, folliculitis, and secondary bacterial infections and thus should be limited to crisis management of eczematous flares for a maximum of 2 weeks [55, 8]. WWT is a safe, effective, and relatively inexpensive therapy for moderate-to-severe AD and should be tried before implementing systemic therapies.

Adjunctive Therapies

Anti-Histamines

Scratching prevents healing of eczematous lesions; thus, disrupting the itch-scratch cycle is a central component of eczema management [8]. Anti-histamines are commonly prescribed to control pruritus; however, evidence-based data demonstrate that it is not effective in AD [56]. Treating the underlying inflammation with TCIs and TCs has a better anti-pruritic effect than systemic anti-histamines [57]. Stress,

irritants (soaps, detergents, scratchy clothing), and excessive sweating can also exacerbate pruritus and thus should be avoided if possible [8].

Antimicrobials

Staphylococcus aureus Colonization and Infection

Although *Staphylococcus aureus* (SA) is a benign colonizer in healthy skin, it can worsen AD by taking advantage of the inherent immunologic and structural dysfunction in the skin of AD patients [58]. Reports estimate that SA skin colonization is present in >90 % of AD patients as compared to approximately 10 % in non-AD individuals; a proportion (11–34 %) of these AD patients are colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) [59]. SA virulence is enhanced in AD due to a combination of factors, including the defective skin barrier, reduced expression of antimicrobial peptides, and secretion of SA superantigens that activate dermal T cells, mast cells, and basophils [59]. Since SA colonization can lead to eczematous flares and an overt infection, empiric decolonization of clinically uninfected lesions may seem reasonable; however, the benefit of such therapies is controversial [60].

A Cochrane review of 21 randomized controlled trials did not find significant *clinical* benefit with antibiotic therapy over other therapies, like TCs and antiseptic baths, in the treatment of SA colonization [60]. Furthermore, discontinuation of antibiotic therapies led to recolonization, raising concern over antibiotic resistance with prolonged therapy [61]. Interestingly, topical anti-inflammatory agents (i.e., TCs, TCIs) can also reduce SA numbers in AD lesions, stressing that optimizing the epidermal barrier not only prevents eczematous flares but also the entry of SA [60, 8]. MRSA-colonized lesions, however, has been associated with resistance to topical anti-inflammatory agents (including TCs) which may be partly due to SA superantigens [59].

Current guidelines reserve the use of systemic antibiotics for clinically infected lesions; however, the use of local antiseptic treatments (i.e., bleach baths) can be considered in AD patients with high SA colonization [8, 61]. Dilute bleach baths are composed of mixing one fourth cup of bleach to a bathtub full of water. Household bleach contains sodium hypochlorite (NaOCl) which produces hypochlorous acid (HOCl) when combined with water. HOCl leads to the generation of superoxide radicals that is cytotoxic to microbes [62]. Ong et al. suggest a treatment regimen with nasal mupirocin (twice daily for 10 days) and dilute bleach baths (daily for 5 days then twice weekly) in conjunction with topical emollients and anti-inflammatory agents for AD patients with MRSA colonization [59]. A randomized trial demonstrated that dilute bleach baths twice weekly and intranasal mupirocin

for a total of 5 days led to significant reduction of eczema symptoms as compared to patients who did not receive these treatments [63, 8].

An overlying bacterial infection, suggested by painful lesions with mucopurulent drainage in an extensive distribution, warrants treatment with antimicrobials [7, 8]. Because of the rising number of MRSA colonization in AD patients, empiric treatment with an anti-MRSA antibiotic is reasonable [64]. The choice of the antibiotic should be guided by antibiotic resistance trend reports in the specific geographic region and/or institution. First-line antibiotic options include oral trimethoprim-sulfamethoxazole (adults 160 mg twice daily) and doxycycline (adults 100 mg once to twice daily) [8]. Although clindamycin is also active against MRSA, resistance is increasing thus this agent is not typically used [65]. Trimethoprim-sulfamethoxazole is safe to use in children but tetracyclines are reserved for patients greater than 8 years old [65]. A culture (i.e., deep wound, nares) should also be obtained to determine the bacterial strain and antibiotic sensitivity [59]. In addition, caregivers and close contacts may be MRSA carriers thus requiring treatment to prevent reinfection of the patient. Alternatively, the penicillinase-resistant penicillins (i.e., dicloxacillin, oxacillin, cloxacillin) and cephalosporins can be used in non-MRSA infected lesions [8].

Viral Skin Infections

Eczema herpeticum (EH) is a disseminated herpes simplex virus (HSV) infection that is observed in AD patients and can be life threatening [4]. An eruption of vesicles, erosions, and/or infected lesions that are refractory to antibiotics should lead to a suspicion of EH [8]. Constitutional symptoms (i.e., fever, lymphadenopathy, malaise) may also be present [66]. Early administration of anti-HSV medications like acyclovir is critical to prevent dissemination and serious sequelae (i.e., keratoconjunctivitis, encephalitis, and meningitis) [4]. Oral acyclovir may be sufficient in mild EH; however, more severe cases require intravenous administration due to better bioavailability [66]. Eye involvement warrants an emergent ophthalmology referral and topical antiviral medications to prevent corneal blindness [66]. Topical anti-inflammatory agents (TCS, TCIs) and oral glucocorticosteroids should be discontinued to prevent suppression of the immune response [66].

Recent investigations have revealed a significant reduction in interferon (IFN) expression in AD patients with a history of EH as compared to those without a history EH [4, 67]. This finding is clinically relevant due to the important role of IFNs in defense against viruses. Reduced levels of IFN regulatory transcription factors, IRF-3 and IRF-7, were also observed in AD patients with a history of EH, suggesting a defect upstream of these signaling pathways [4]. These observations

provide an opportunity to identify EH-susceptible AD patients and to develop future therapeutic targets.

Other viral skin infections, like warts and molluscum contagiosum, can also be observed in AD patients and may be more severe due to the underlying immune defects in viral defense [8]. Affected areas should be covered to prevent transmission to other individuals and may require treatment with cryotherapy, manual curettage, and/or topical agents like imiquimod [66].

Vitamin D

Vitamin D plays an important role in epidermal differentiation and barrier function through the regulation of calcium, antimicrobial peptides (i.e., cathelicidin), and TOLL-like receptors [68–70]. Interestingly, there is an increased prevalence of AD in regions with high latitudes [71, 72] and lower ultraviolet (UV) exposure [73] which suggests an increased likelihood of vitamin D deficiency in this specific population. Several studies have demonstrated that vitamin D supplementation has led to improvement of AD symptoms, particularly AD that worsens in the winter [74–76].

A recent randomized, controlled study in Mongolia has shed further insight into the potential use of vitamin D in AD [77]. Mongolia's (latitude 48 ° N) long winters and limited availability of vitamin D-rich and fortified foods favor a population with an increased likelihood of vitamin D deficiency [78]. A 1-month trial of vitamin D supplementation (1000 IU) in 107 children with AD that worsened in the fall-to-winter transition revealed a significant improvement of AD symptoms. This was independent of TCs use. Limitations of this study included the lack of baseline serum vitamin D levels (due to limited funds) and a low dose of vitamin D that is unlikely to treat vitamin D deficiency over a 1-month interval. Although the results are promising, further studies are needed to investigate the role of vitamin D supplementation in AD.

Difficult-to-Treat Atopic Dermatitis

Treatment Compliance

AD that is not responding to topical therapies should prompt the physician to assess for compliance with the treatment regimen before considering use of systemic medications. Non-compliance is responsible for more than 50 % of treatment failures in AD [79–81]. The reasons for non-compliance include (i) running out of the medication and not getting it refilled; (ii) misunderstanding the correct frequency and type of medication that should be applied; (iii) ineffective application of medication; (iv) lack of motivation; (v) impression that treatments do not work; (vi) undesirable side effects (i.e., oily skin from emollients); and (vii) medication is too painful to

apply [7]. Another important component of AD management is patient/parent education on the chronicity of AD and correct application of topical treatments [8]. Because a treatment regimen may involve several different agents, written action plans should be used to reinforce the treatment plan at home [7].

Alternative Diagnosis

An alternative diagnosis, other than AD, should also be considered in cases of difficult-to-treat eczemas. Clinical features that suggests an alternative diagnosis include rashes that are non-pruritic or with an atypical distribution or onset in adulthood [7]. Medical conditions that mimic AD include primary immunodeficiency disorders, primary metabolic conditions, skin infection, drug reactions, malignancies, and other primary skin conditions (i.e., psoriasis) [7].

Allergic and Irritant Contact Dermatitis

Preservatives and active ingredients in topical medications can complicate the management of AD through development of an allergic or irritant contact dermatitis [82]. When suspected, patch testing should be performed to evaluate for contact allergy especially to TCs and components of the patient's emollients.

Food and Aeroallergens

Food-induced eczematous flares are more common in children than in adults and should be considered in children with moderate to severe eczema despite optimal medical management [7]. The most commonly associated food allergens are cow's milk, egg, soy, and peanut, triggering an eczematous flare either through an immediate or delayed type hypersensitivity reaction [83]. The latter makes the diagnostic evaluation challenging as skin prick testing (SPT) and specific IgE testing may lead to false-negative results [7]. Furthermore, false-positive results may also occur due to the low specificity of SPT and specific IgE testing, and elevated IgE levels in AD patients [83].

Food atopy patch testing (APT) evaluates for the presence of delayed hypersensitivity reactions. Because of limited data and no test standardization, the report of the NIAID-Sponsored Expert Panel in the Guidelines for the Diagnosis and Management of Food Allergy in the USA recommends that APT should not be used in the routine evaluation of non-contact food allergy [84–86].

Because of the likelihood of false-positive results, foods that test positive during the work-up should be evaluated for clinical relevance through an elimination diet for 4 to 6 weeks [83]. A food diary may also be helpful if the work-up fails to determine a food allergen and there is high suspicion for a

food-related AD [83]. Unselected elimination or elemental diets, however, are not beneficial and may lead to nutritional deficiencies [87]. Once AD symptoms improve, an oral food challenge should be performed within 6–12 months as food-related AD usually resolves with time [83].

Aeroallergen-induced AD flare is more common in adults and also occur through both an immediate and delayed type hypersensitivity reaction. Evaluation of aeroallergen allergy involves standard SPT and IgE-specific testing. Due to similar limitations in food APT, APT with aeroallergens is not currently recommended for routine clinical practice [88]. Exacerbations of eczema and pruritus have occurred with bronchial and intranasal challenge as well as direct contact with aeroallergens [89]. Standard avoidance measures can lead to improvement of AD symptoms, which has been demonstrated with dust mite allergen [8].

Systemic Immunosuppressants

A small proportion of patients with refractory AD can be managed with second-line therapies that include immunosuppressive drugs and phototherapy.

Cyclosporine

Cyclosporine, an oral calcineurin inhibitor, is recommended as first-line short-term therapy for severe AD [90]. Several randomized controlled studies have demonstrated that both children and adults with severe AD benefit from oral cyclosporine [91–93]. Like TCIs, cyclosporine also inhibits gene transcription in cells. A recent study by Khattri et al. demonstrated that cyclosporine reduced the expression of IL-13, IL-22, and S100s messenger RNA (mRNA) which all modulate the inflammatory process in AD [94]. IL-22 inhibits epidermal differentiation and induces hyperplasia through up regulation of S100s protein [95–97]. Investigators found that a reduction of cytokine expression was coupled with a reduction in epidermal thickness and an increase in epidermal differentiation proteins. Study patients reported a decrease in their AD symptoms by more than 50 % by the second week.

Cyclosporine is usually dosed at 5 mg/kg/day; however, since adverse effects are dose-dependent, therapy can start at lower doses (3 mg/kg) and up-titrated to a minimum effective dose [7, 90, 8]. Therapy should be discontinued within 6 months but can be extended for up to 1 year; however, long-term safety data are limited [7, 90]. Discontinuation of cyclosporine is associated with relapse of symptoms [8].

Although lacking the side effects associated with long-term systemic corticosteroids, cyclosporine should also be used with caution due to serious side effects of hypertension, hyperbilirubinemia, renal impairment, hypertrichosis, and paresthesia [8]. Baseline and routine laboratory testing should be done to monitor for these side effects.

Azathioprine

Azathioprine has been recommended as second-line treatment for severe AD [90]. It is a purine analog which is metabolized to 6-mercaptopurine and incorporated into replicating DNA thus inhibiting DNA synthesis. This effect is limited to lymphocytes because they lack DNA salvage pathways [98]. Studies have demonstrated that azathioprine leads to an overall decrease in AD severity through its anti-proliferative effects [90].

The main side effect of azathioprine is profound myelosuppression. A baseline level of thiopurine methyltransferase may predict individuals who are susceptible to this adverse effect [99, 8]. Like cyclosporine, discontinuation of azathioprine can lead to relapse of symptoms [7].

Methotrexate

Methotrexate, a folic acid antagonist, is recommended as third-line treatment for severe AD [90]. Similar to azathioprine, methotrexate interrupts purine and pyrimidine synthesis which are essential components for DNA and RNA production. Results from a small trial demonstrated that methotrexate was as effective as azathioprine [100]. Symptom improvement occurs as early as 2 weeks into therapy and lasts for up to 3 months [8]. Patients who do not respond by 3 weeks of methotrexate therapy (15 mg per week) are unlikely to improve with higher doses [8]. Therapy should thus be discontinued to limit side effects which include impairments in the liver, lungs, kidneys, and bone marrow.

Systemic Corticosteroids

Systemic corticosteroids are the most frequently prescribed therapy for severe AD [8]. Prolonged use of systemic steroids, however, should be avoided due to the risk of serious side effects [101, 8]. Although a short course of steroids may be beneficial to treat an acute eczematous flare in certain situations, discontinuation of the medication often leads to a rebound of eczema symptoms [101, 8]. A comparison study with oral prednisolone and cyclosporine revealed a higher rebound rate upon discontinuation of prednisolone despite use of mid-potency TCs and emollients [102]. To prevent rebounding of symptoms, oral corticosteroids should be tapered slowly and coupled with an aggressive regimen of topical agents [8].

The risk of developing serious side effects from systemic steroids increases with higher doses (greater than an equivalent of prednisone 10 mg daily) and longer duration of use [103]. The effect of steroids on the skin (i.e., atrophy, easy bruising) and HPA axis was previously discussed in the TCs section. Other systemic effects include the risk of developing osteoporosis, cataracts, cardiovascular disease, impaired

glucose metabolism, gastritis, and immunosuppression. Consideration of these serious effects is important when prescribing oral steroids to patients with these preexisting clinical conditions. Because of its limited effectiveness in the treatment of AD and the risk of serious side effects, systemic steroids should be used rarely and sparingly in AD [8]. The limited systemic absorption from TCs, as mentioned in the TCs section of the article, favors this route of administration to gain its potent anti-inflammatory effect.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) blocks the purine biosynthesis pathway and, like azathioprine, its anti-proliferative effect is specific to lymphocytes due to lack of a DNA salvage pathway. Although not FDA-approved for AD, MMF has been used off-label as an alternative therapy option for severe AD [104].

Results from several studies have shown a benefit of MMF in AD [104]. One study demonstrated that although initial symptom improvement was delayed with MMF as compared to cyclosporine, symptom remission lasted longer in MMF-treated patients upon discontinuation of medications [105, 104]. A small retrospective study with children found that it was also effective and well tolerated although there are no long-term safety or efficacy data [106, 104].

There are no recommendations for the optimal dose and duration of MMF therapy in AD. Common side effects are gastrointestinal-related (nausea, vomiting, abdominal cramps), myelosuppression, skin cancer, and lymphoma [104].

Interferon Gamma

Interferon gamma (IFN- γ) is a cytokine released from the TH1 immune pathway, leading to down regulation of the TH2 response that fuels AD. It is recommended as an alternative treatment option in patients with severe AD [8]. Several studies have demonstrated the effectiveness of IFN- γ over placebo in AD; however, there are no current recommendations for the optimal dose and duration of therapy [107, 108, 104]. Side effects include constitutional symptoms (fever, fatigue, nausea, vomiting, and myalgias) and baseline and serial monitoring of complete blood counts, renal and hepatic function serologies, and urinalysis are recommended every 3 months during therapy [107, 104].

Phototherapy

Phototherapy is a second-line therapy for severe AD and should be administered by physicians who are experienced with this type of treatment [7]. There are multiple forms of phototherapy; however, the most commonly used modalities are narrow band ultraviolet (UV) B, broadband UVB, and

UVA [8]. Phototherapy suppresses the immune response in atopic skin, improves the integrity of the epidermal barrier, and reduces skin colonization with microbes, including *S. aureus* [109].

Common side effects of phototherapy are skin erythema, pain, pruritus, and pigmentation. Melanoma, non-melanoma skin cancer, folliculitis, photo-onycholysis, and herpes simplex virus reactivation have also been reported albeit less commonly. There are also side effects that are specific to each form of phototherapy, i.e., cataract formation with UVA therapy [104].

There are limited comparison studies between the different types of phototherapy; however, a systematic review found no difference between UVA and narrowband UVB therapy in terms of pruritus, clinical, and quality of life scores [109]. Narrowband UVB, however, is preferred in adults and recommended as first-line phototherapy in children due to its safety profile [104]. The long-term effects in children are not known, however an increased risk of non-melanoma skin cancer has been reported in children who underwent phototherapy for psoriasis [110, 104]. It is unclear if results from this study can be extrapolated to children with AD.

Although current studies show that phototherapy is an effective treatment in AD, more investigations are needed to evaluate the optimal duration of therapy, the long-term consequences, and remission rates.

Novel Therapies

Advances in research have led to new insights into the immunologic mechanisms involved in AD, paving the way for immunological-based therapies.

Omalizumab

Omalizumab is a monoclonal anti-IgE antibody that binds to free IgE in serum and is FDA-approved for the treatment of severe asthma and chronic idiopathic urticaria. Atopic individuals generally have elevated levels of IgE and it is hypothesized that lowering the levels of IgE can reduce skin inflammation and lead to symptom improvement in AD [111]. The results of omalizumab therapy in AD patients, however, have been variable.

One study demonstrated no improvement in AD symptoms despite reduced levels of free IgE, surface-bound IgE, and FcεRI expression [112]. Another study demonstrated improvement in AD symptoms that lasted for up to 2 months after omalizumab discontinuation [113]. Interestingly, patients had a baseline serum IgE level of ≥ 5000 IU/mL which was unlikely affected with the dose of omalizumab administered during the trial (300 mg every 2 weeks for 4 months). This suggests that omalizumab may work independently of an IgE-

mediated process in AD [114]. A recent prospective study found that omalizumab responders had higher baseline levels of glycerophospholipids and a lower sphingomyelin/total phosphatidylcholine ratio, suggesting that these patients did not carry the filaggrin mutation [115]. Based on these observations, the investigators suggested that patients with a primary defect in the epidermis (i.e., filaggrin mutation) would be less likely to respond to omalizumab therapy. Patients in this study received omalizumab 150 mg every 2 weeks for 7 months regardless of baseline IgE levels. These investigations show promise in omalizumab therapy in AD; however, more studies are required to confirm its efficacy and to determine appropriate candidates for therapy. The role of omalizumab in the treatment of AD has not been established at this time.

Rituximab

Rituximab is an anti-CD20 antibody that targets mature and immature B-lymphocytes for destruction. A study involving six patients with severe AD who were treated with two doses of Rituximab (1000 mg every 2 weeks) noted a significant improvement in AD symptoms [116]. The levels of CD20+ cells were reduced in both serum and eczematous lesions. T cells, IL-5, and IL-13 were also reduced in the skin. These results, however, were not reproducible in a subsequent study though a significant limitation may have been the sample size with only two patients [117].

Allergen Immunotherapy

Aeroallergens can trigger AD and patients with a confirmed allergy may benefit from immunotherapy [8]. Immunotherapy is effective in treating allergic rhinitis by modifying the immune reaction from a predominant TH2 to a TH1 response. This mechanism may also help patients with moderate to severe AD. A systematic review of seven studies, however, demonstrated inconsistent results with immunotherapy in AD [118]. This was mainly due to poor study design and different AD symptom scores. Dust mite-allergic patients, however, reported improved SCORAD scores after dust mite immunotherapy [8]. Thus current guidelines in the 2012 practice parameter update on atopic dermatitis state that dust mite immunotherapy can be offered to this particular patient population [8]. More studies are warranted to determine the benefit of immunotherapy for other aeroallergen allergies.

Conclusion

The management of AD involves a variety of interdependent factors that all contribute to improving the quality of life in AD patients. Although topical anti-inflammatory agents and

moisturizers are the mainstay treatments, compliance and patient education are also crucial to symptom improvement. Unique therapies, such as bleach baths and WWT, have also been found to be beneficial adjunct therapies. The complexity of the immunopathologic mechanisms in AD has also uncovered new potential targets in AD therapy including vitamin D supplementation, omalizumab, rituximab, and allergen immunotherapy. Further investigations, however, are needed to elucidate the role of these medications in AD management.

Summary

- Increasing skin hydration with moisturizers is the cornerstone for AD treatment. A recommended regimen involves warm, soaking baths for at least 10 min followed by application of moisturizers onto damp skin.
- Maintenance therapy with low-potency topical corticosteroids with twice weekly application to previously affected areas prevents eczematous flares. Short-term use of high- and intermediate-potency TCs can be used for acute eczema flares.
- Topical calcineurin inhibitors are approved for short-term use and intermittent long-term use in children (>2 years old) and adults. These agents are preferred for facial and eyelid eczema due to its low side effect profile (as compared to topical corticosteroids).
- Wet wrap therapy can be used as crisis management for moderate-to-severe AD flares but should be limited to 2 weeks duration to avoid folliculitis, maceration and secondary bacterial infection.
- Scratching can perpetuate the progression of AD so disrupting the itch-scratch cycle with anti-histamines can be considered. Other measures include avoidance of abrasive clothing/detergents/soaps and controlling temperature/humidity in the environment.
- Clinically infected lesions with an extensive distribution should be treated with systemic antibiotics. Local antiseptic treatments (ie. bleach baths) can be considered in AD patients with high SA colonization.
- Difficult-to-treat AD should prompt an investigation into the compliance to the treatment regimen, an alternative diagnosis (especially in older adults) and an overlying irritant or allergic contact dermatitis (including but not limited to topical corticosteroid allergy).
- Systemic immunosuppressants are reserved for AD refractory to standard therapies: cyclosporine, azathioprine, methotrexate, interferon gamma, and phototherapy. These agents have serious side effect profiles which warrant careful monitoring.
- Systemic corticosteroids can treat eczematous flares effectively; however, rebound is common with discontinuation of therapy. Because of the serious side effect profile and limited effectiveness, systemic corticosteroids should be used rarely and sparingly. An aggressive topical medication regimen should be used during the slow taper of corticosteroids to prevent a rebound of symptoms.
- Immediate and delayed hypersensitivity to foods can lead to eczema exacerbations, especially in children. Foods that test positive during a work-up or are highly suspicious can be eliminated to monitor for any signs of eczema improvement. These foods can then be restarted, one at time, to determine if there is a recurrence of eczema symptoms. An oral food challenge is the gold standard for the diagnosis of food allergy in AD.
- Exacerbation of eczema due to aeroallergens is more common in adults. The use of aeroallergen immunotherapy in AD is still in its infancy and more studies are required to demonstrate its effectiveness. Dust mite immunotherapy, however, has been successful in reducing eczema symptoms in dust mite-allergic AD patients and can be considered.
- Potential immunomodulatory agents (i.e., omalizumab and rituximab) may be used for AD treatment in the future though further trials are warranted to demonstrate their benefit.

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