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Therapeutic Options

DERMATOLOGY FOCUS: ATOPIC DERMATITIS

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BACKGROUND

Atopic Dermatitis (AD), also known as eczema, is a chronic, inflammatory skin disease involving dryness and pruritis. Onset often occurs in early childhood, usually with an onset before the age of five years. Although children may outgrow AD, many adults are also affected. Left untreated, AD can lead to a significant decrease in quality of life, as well as secondary infections and sleep loss.[1,2] In addition, AD can remain in a chronic, active state if treatment is not optimized. AD is also known to be associated with other atopic conditions such as food allergies, asthma, and allergic rhinoconjunctivitis.[1] A survey by the Eczema Society of Canada found 91% of respondents living with AD felt their condition was not well controlled.[3]

ETIOLOGY & PATHOPHYSIOLOGY

Worldwide, AD affects between 5-20% of children.[4] Most cases of onset occur before the age of five (nearly 85% of cases), with 60% of cases occurring in the first year of life; severe disease is associated with AD onset occurring in the first 6 months.[4,5] There is limited prevalence data for AD in adults, but based on evidence from studies it is estimated to be 7-14%.[4,6] Globally, the last few decades have shown an increasing trend in the prevalence of AD.[4]

There are multiple factors involved in the development of AD. These include skin barrier dysfunction, immune dysregulation, unbalanced skin microbiome, genetic factors, and inflammatory triggers from the environment.[1,4] The stratum corneum is the skin's first line of defence, typically made of corneocytes and keratin filaments in a matrix of ceramides, cholesterol, free fatty acids, and filaggrin breakdown products. In AD, the stratum corneum may be more permeable, have decreased water retention, increased transepidermal water loss, or have altered lipids. This epidermal barrier dysfunction is a primary concern in AD pathophysiology and is caused by numerous factors such as abnormal tight junctions, decreased filaggrin production, microbial colonization, proinflammatory cytokine release, and the itch-scratch cycle.[4]

Genetically, a major factor in defective barrier function is filaggrin deficiency. Profilaggrin is the precursor to filaggrin and is encoded by the *FLG* gene. For AD, the strongest genetic risk factor is loss-of-function *FLG* variants, the prevalence of which varies by geography and ethnicity. Other genes implicated in AD have also been found, including those responsible for innate host defences and T-cell functioning.[4]

Both innate and acquired immune responses have inflammatory roles in AD. Stimulation of toll-like receptors is responsible for the release of danger signals (alarmins), such as antimicrobial peptides (AMPs), proteases, cytokines, and extracellular matrix proteins, upon disruption to the epithelial barrier. This activates type 2 immune cells (such as mast cells, Th2 cells, and basophils) as well as inflammatory dendritic epidermal cells. The chronic itch associated with AD is due to intricate interactions between keratinocytes, Th2 immune cells, and non-histamine-sensitive peripheral C-nerve fibers.[4]

In most AD patients, their skin microbiome is considerably altered with decreased bacterial diversity and *Staphylococcus aureus* (*S. aureus*) overgrowth – nearly 100% of these patients are colonized with *S. aureus*.[4] Interestingly, a decrease in microbial diversity and an increase in *S. aureus* on the skin has been found during eczematous flares, with the microbiome returning to normal after AD treatment.[7] AD patients are predisposed to bacterial and viral skin infections, including impetigo, and disease exacerbation due to these infections. However, it is important to note that methicillin-resistant *S. aureus* (MRSA) infection is uncommon in children with the condition.[4]

RISK FACTORS

Approximately 70% of AD patients have a family history of atopy (allergic rhinitis, asthma, or eczema), the strongest risk factor for AD. In addition, loss-of-function variants in the *FLG* gene, also a major AD risk factor, is associated with a three- to four-fold increased risk of AD.[4]

Environmental triggers such as cold and dry climates, air pollution, water hardness, and allergies can contribute to AD exacerbation, as well as other triggers such as dyes or scents in soaps or lotions, detergents, chemicals, household cleaners, long hot showers, and rough clothing materials.[4,8] Itching can be worsened by sweat, stress, and overheating.[1]

SIGNS & SYMPTOMS

Depending on age, ethnicity, and severity of disease, the clinical presentation of AD varies.[1,4] Principle signs and symptoms are dry skin and severe itch, with ill-defined patches of redness and scales.[1,4,5] Appearance may also include small dotted bumps, patches of skin flakiness, or colour changes to affected skin; skin may appear red or pink in individuals with light skin, and dark brown, purple, or gray in patients with dark skin.[5] Eczema can present as acute (sometimes called a flare), with intense itchiness, red papules or vesicles, oozing, or crusting; or as subacute/chronic with dry, scaly lesions or excoriated red papules.[2,4] Chronic scratching can lead to skin thickening ("lichenification") as well as fissures.[1,4] In severe cases, any area of skin may be involved, although AD is less common in axillary, gluteal, or groin areas. Presence of symptoms in these areas may indicate alternate diagnoses such as psoriasis or contact dermatitis.[4] For typical patterns of presentation based on age, see Table 1.

PHARMACOTHERAPY

AD is chronic and relapsing over months to years, with intermittent flares and remission.[4] As there is no cure for AD, goals of therapy are to reduce symptoms (pruritis, dryness, and inflammation), prevent exacerbations, and reduce the risk of secondary infection.[1,2] Since symptoms vary between patients and AD disease course is variable, treatment should be individualized and chosen based on severity and response to therapy.[9] If the diagnosis is uncertain, the condition is unresponsive to therapy, or high-potency treatment on delicate areas or systemic treatments are being considered, referral should be made to a specialist.[2]

TREATMENT OF ACUTE AD

The foundation of AD treatment involves a combination of skin barrier repair and hydration with emollients, in addition to topical anti-inflammatory therapy. Topical anti-inflammatory options include topical corticosteroids (TCs) or topical calcineurin inhibitors (TCIs); both are effective at controlling pruritis.[2] For mild disease, first-line therapy is the use of unmedicated moisturizers applied liberally at least once daily.[1,10] Ensuring enough moisturizer has been applied is more important than the choice of moisturizer, although ointments may be less irritating than creams or lotions.[1] If moisturizers are ineffective, a low-potency TC cream or ointment can be used in addition to emollients applied throughout the day.[2] For moderate or severe disease, moisturizers in addition to topical anti-inflammatory therapy are still tried before considering phototherapy or systemic anti-inflammatory treatment.[10] See Table 2 for topical therapy options in AD.

Topical Anti-Inflammatory Therapy

TCs provide symptomatic relief of both acute and chronic inflammation and pruritis in adults and children with AD.[11,12] These synthetic cortisone derivatives act quickly and effectively, providing anti-inflammatory, anti-proliferative, vasoconstrictor, and immunosuppressive effects.[1,11] TCs are classified by potency and choice should be based on age, severity of condition, and body area involved.[2]

Low-potency TCs are generally more appropriate for mild cases of AD, whereas medium to high potency TCs may be needed for moderate AD cases.[2] High potency and very high potency TCs should not be used longer than 4 weeks continuously, due to the chance of systemic side effects.[13] Potent TCs are generally avoided on delicate facial/fold areas but may be used briefly (5-7 days) for a rapid response, and then stepped-down to a lower potency option after this time.[2] Acute flares may need high or very high potency TCs for up to 2 weeks, followed by gradual reduction in potency and application frequency to prevent rebound dermatitis.[2,11] Facial areas and intertriginous folds absorb topical therapy more easily as the skin is thin, thus low potency TCs are generally more appropriate. For body areas or scalp where skin is of medium thickness, medium potency TCs can be used. For thicker skin areas such as the palms and soles of the feet, high potency TCs are typically recommended.[1]

Comparison of once daily to more frequent application of potent TCs has made little difference in clinical outcomes or adverse events; therefore, these are usually dosed once or twice daily. Milder TCs may be applied 2-3 times daily for more effect.[1,11,13] TC treatment should be continued until rash and itch are resolved, which may take from a few days to several weeks.[1] If a lesion has not improved after 2-4 weeks of treatment, a physician should be consulted.[1,9]

Issues with long-term TC use include the potential for adrenal suppression, especially with very high potency therapy on large body areas, and other side effects such as telangiectasias, folliculitis, and skin thinning.[2] However, systemic adverse effects from TCs are rare and usually due to misuse. The risk of skin atrophy increases with higher potency TC use, longer duration of treatment, and use in the elderly who have thinner skin.[11]

The **TCIs** tacrolimus ointment (Protopic®) and pimecrolimus cream (Elidel®) are used for acute and chronic AD as well as maintenance therapy in both adults and children. These are non-steroid immune modulators with a more targeted anti-inflammatory mechanism than TCs, but tend to be slower acting, usually requiring twice daily dosing.[1,12] TCIs are considered second-line therapy for intermittent treatment or in patients unresponsive to other therapy, but have been used (off-label) as a first-line option on delicate areas such as the face, eyelids, neck, or folds, or in combination with TCs elsewhere on the body. Tacrolimus is thought to be more effective than pimecrolimus, however some patients may better tolerate the latter.[1,2] Tacrolimus is considered

Table 1. Common Presentation Patterns of Atopic Dermatitis.[1,4,5]

Age Group	Affected Area(s)	Presentation
Infants Babies and children < 2 years	Facial, extensor	• Front of arms and legs • Cheeks, scalp • Itchy, red, scaly, crusted lesions[4,5]
Children/ Adolescents (ages 2-16 years) Adults	Flexural, fold	• Sides of neck • Elbow creases, back of knees • **Ages 2-16:** less exudation, lichenified plaques present in flexures (wrists, neck, ankles, antecubital and popliteal fossae) • **Adults:** wrists, hands, forearms, face[4,5]
Adults	Facial, hand	• Localized • Lichenified • Face, neck, hands[1,4]

equal in strength to a medium potency TC.[2] Possible side effects from TCIs include transient burning, redness, or itching, and short-term safety has been confirmed.[1,2] There have been reports of skin malignancy and lymphoma in patients using TCIs, although a causal relationship has not been proven.[14] TCIs are not recommended for continuous long-term use, or for use in patients who are under 2 years of age or who are immunocompromised.[2]

A new class of topical anti-inflammatory AD treatment, crisaborole 2% ointment (Eucrisa®) is a **topical phosphodiesterase 4 (PDE4) inhibitor** approved for mild to moderate AD in patients over 3 months of age.[1,2,15] Early studies have demonstrated improvement in symptoms of AD, particularly pruritis, but crisaborole does not yet have a defined place in therapy; head-to-head studies with established AD treatments are needed. To date, crisaborole has been associated with mild adverse effects (mainly application site pain, paresthesia) and is considered generally safe for long term use.[2]

Phototherapy and Systemic Immunomodulatory Therapy

After an optimal course of topical treatment, persistent moderate to severe AD may require phototherapy or systemic medication for disease control.[2,9,12] Phototherapy is not suitable for use in infants or young children, but may be considered for acute or chronic AD in older pediatric or adult patients. Narrowband ultraviolet B (NB-UVB) is the most common phototherapy used, as it is readily available and effective with a low-risk profile.[2,12] Phototherapy can be used alone or in combination with other topicals if appropriate.[12]

Systemic therapy options include oral corticosteroids, calcineurin inhibitors (e.g. cyclosporine), or immunosuppressive agents (methotrexate, azathioprine, mycophenolate mofetil); although effective, the latter two groups are considered off-label uses for AD.[9] When used for AD, these therapies should be highly individualized based on risk-benefit and patient preference. The lowest effective dose should be used, particularly as these options are associated with severe adverse effects and require close monitoring.[12,18] Corticosteroid systemic therapy is typically only used for a severe acute flare or as short-term bridging to another systemic treatment.[1,12]

Table 2. Topical Pharmacotherapy for Atopic Dermatitis.[1,11,13,15,16,17]

Drug Class†	Examples‡	Place in Therapy	Comments
Topical Corticosteroids – LOW Potency	Hydrocortisone 0.5%, 1%, 2.5% Desonide 0.05%	• Mild AD • Preferred for sensitive areas (face, neck, skin folds, groin)	• Safe and effective when used correctly
Topical Corticosteroids – MEDIUM Potency	Beclomethasone dipropionate 0.025% Clobetasone 17-butyrate 0.05% (OTC) Mometasone furoate 0.1% Hydrocortisone 17-valerate 0.2%	• Mild to moderate AD • For use on most body areas; caution on face, neck, skin folds	• Safe and effective when used correctly • Rarely used on groin or eye areas ◦ Some formulations of fluocinolone acetonide (e.g. Derma-Smoothe/FS®) contain peanut oil
Topical Corticosteroids – HIGH Potency	Amcinonide 0.1% Fluocinonide 0.05%	• Moderate to severe AD • Thick, lichenified plaques • Palms, soles of feet	• Safe and effective when used correctly • Rarely used on face, neck, groin or skin folds
Topical Corticosteroids – VERY HIGH Potency	Betamethasone dipropionate glycol 0.05% Clobetasol 17-propionate 0.05%	• Severe AD • For thicker-skinned areas (palms, soles of feet)	• Safe and effective when used correctly • Close monitoring for adverse effects such as striae, atrophy, telangiectasia, purpura, or suppression of HPA axis (adverse effects more likely with incorrect use of high or very high potency products)
Topical Calcineurin Inhibitors (TCIs)	Pimecrolimus 1% Tacrolimus 0.03%, 0.1%	• Pimecrolimus for mild to moderate AD; tacrolimus for moderate to severe • Second line therapy • May be used on all skin areas	• Transient burning/tingling sensation at site of application; skin tolerance develops after a few days • Not for use in immunocompromised patients
Phosphodiesterase 4 Inhibitors	Crisaborole 2%	• Mild to moderate AD • May be used on all body areas except mucous membranes • Evidence comparing efficacy to TCs or TCIs is lacking	• For patients > 3 months of age

† Different publications may have slightly varied TC potency categories; vehicles also affect potency; rankings are more of a guide. Potency can also be classified in groups ie. group I (highest) to VII (lowest).[17]

‡ Various formulations may be available such as gel, solution, lotion, cream, ointment, shampoo, foam. This is not an all-inclusive list of potential therapeutic options; only select examples from each drug class are provided.

Dupilumab (Dupixent®), a newer systemic AD treatment approved in Canada, is a subcutaneous injection given every 2 weeks.[2,19] Dupilumab is a human monoclonal antibody intended for moderate to severe AD in patients aged 6 years and over, with or without TCs.[2,19,20] Long term safety data is lacking.[2,19]

Emerging Therapies

A newer class of systemic treatment approved in Canada for AD are biologics, which are usually given as a subcutaneous injection every 2 weeks. Dupilumab , for ages 6 and over) and Tralokinumab (for ages 18 and over) are first-line therapies for patients with moderate to severe AD which is not controlled by topical therapies.[2,19,20,21,22] A systematic review of 149 RCTs evaluating 75 interventions in 28,686 patients revealed that compared with continued standard topical treatment alone, adding dupilumab and tralokinumab led to large improvements in multiple patient-important outcomes.[21,22] Dupilumab and tralokinumab are effective as monotherapy, but both can also be used with topical treatment as combination therapy.[21] Long term safety data is lacking.[2,19]

In recent years, Health Canada has also approved two oral JAK inhibitors (abrocitinib 100-200 mg and upadacitinib 15- 30 mg) for age 12 years or above with moderate-severe AD refractory, intolerant, or unable to use mid- to high potency topical treatment and systemic treatment.[21,23,24] There may be specific exceptional scenarios where patients will place a high value on very short-term (days) use of oral JAK inhibitors, such as in the case of a rare and severe flare, for special social circumstances or a brief bridge to safer systemic therapies (e.g., dupilumab or tralokinumab).[21]

A topical JAK inhibitor, ruxolitinib 1.5% cream, was approved in September 2021 by the U.S. FDA. Indicated for immunocompetent patients over 12 years of age, ruxolitinib is intended for short-term therapy of mild to moderate AD if TCS and TCI do not yield sufficient control.[2] Concerns about systemic absorption with topical JAK inhibitors are sufficient to limit application of ruxolitinib to less than 20% BSA and use it in a discontinuous manner as decrease the potential for harm.[21,24]

PREVENTION OF AD FLARES

Maintaining the integrity of the skin barrier is key in eczema prevention, and this can be accomplished with regular use of moisturizers at least once daily to prevent flares.[1,2,9,12] After a moderate to severe AD flare has stabilized, proactively continuing a TC or TCI intermittently (2-3 times weekly) over the long-term to previously affected skin may help prevent a relapse.[1,2,11,12] Determining and avoiding environmental irritants or triggers as mentioned previously is also important for prevention.

NONPHARMACOLOGIC INTERVENTIONS

Moisturizers can help with both maintenance therapy and flare prevention for AD patients.[12] Preference should be given to thick creams with low water content or ointments such as petroleum jelly, as these formulations protect best against dry skin.[2] In addition, these products should be hypoallergenic and fragrance free.[12] Bathing should be brief, in warm (not hot) water, with liberal amounts of moisturizer applied within 3 minutes of light drying.[1,8,12] Bleach baths (mix one-half cup of household bleach in a full tub of water, soak for ten minutes, then rinse thoroughly with clean water, two or three times per week) can be considered to decrease inflammation and reduce skin bacteria, however evidence regarding effectiveness when compared to bathing with water is limited.[21,23,24] Reducing skin damage from itching can be managed by keeping nails short and clean, and wearing cotton gloves to sleep.[8]

SUMMARY

Multiple factors are involved in AD pathology. Moisturizers, TCs, and TCIs, and/or crisaborole may be used to treat and prevent flares; systemic treatments are options when phototherapy or topical treatments have not controlled moderate to severe eczema.[19] Patients with AD often experience a decrease in quality of life and suffer with secondary infections and sleep loss. As a chronic relapsing and remitting disease, educating patients (and their parents if applicable) about this condition is imperative for optimal AD management, to improve adherence to therapy and implement flare prevention strategies.

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