

Atopic Dermatitis

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Goals and Objectives

Goals:

To provide the pharmacist with an understanding of the pathological and clinical features of atopic dermatitis and the latest approaches to its treatment.

Objectives:

After completing this article, the pharmacist should be able to:

1. Discuss the clinical features of common dermatitis-related conditions of the skin.
2. Describe the epidemiology, pathology, and clinical presentation of atopic dermatitis.
3. Discuss treatment options for atopic dermatitis.
4. Describe the role of the pharmacist in the management of patients with atopic dermatitis.

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Atopic dermatitis is one of a number of inflammatory skin conditions that are classified as eczematous dermatitis. In addition to the typical inflammatory features observed in these disorders, such as erythema (redness), and pruritis (itching), the use of the descriptive term eczema (Greek “to boil over”) reflects the common presence of weeping, crusted, and/or scaly papules (small, solid raised lesions) or vesicles (small, fluid-filled eruptions). Skin conditions that are considered under the dermatological realm of dermatitis, eczema, or eczematous dermatitis include:

Atopic dermatitis: A chronic inflammatory condition of the skin that often develops in infancy or childhood, characterized by red, weeping, crusted vesicular eruptions and persistent, intense pruritis, and many patients have a personal or family history of asthma or allergic rhinitis.

Contact dermatitis: Allergic contact dermatitis is a delayed hypersensitivity reaction of the skin to specific allergens, such as latex, nickel-containing jewelry, and the oily resin of poison ivy, in which patients present with erythematous, pruritic papules and vesicles; irritant contact dermatitis involves toxicity and damage to the skin resulting from exposure to irritating substances, such as chemicals, in which patients present in a similar manner as in allergic contact dermatitis except for complaints of burning instead of pruritis.

Drug-related eczema: Inflammatory eruptions in the skin that result from the systemic administration of drugs that act as antigens or haptens, such as penicillin or sulfonamide antibiotics.

Dyshidrosis: The development of scaly, peeling, erythematous patches on the fingers and palms secondary to frequent handwashing.

Nummular dermatitis (discoïd eczema): An inflammatory condition of the skin precipitated by extreme dryness of the skin, in which patients present with characteristic erythematous, pruritic, scaly, circular (coin-shaped) patches commonly on the legs and arms.

Photoeczematous eruption: Inflammatory eruptions in the skin triggered by exposure to ultraviolet light in the presence of a pre-existing topical or systemic antigen.

Seborrheic dermatitis: An inflammatory condition of the skin that may result from overgrowth of the yeast *Pityrosporum ovale*, in which patients present with erythematous, greasy, scaly patches, particularly at the creases of the nose and nasolabial folds, forehead, eyebrows, and scalp.

Focus on Atopic Dermatitis

Epidemiology

Atopic dermatitis is one of the most common dermatological conditions of infancy and early childhood. In the U.S., an estimated 10-20% of infants and children have signs and symptoms consistent with atopic dermatitis. About 65% of patients are diagnosed with atopic dermatitis in the first year

of life (often within the first 6 months) and 90% are identified by age five. Adult onset is relatively rare. Although many patients experience clinical remission, or at least a decreased frequency and severity of symptoms by the adolescent years, it has been estimated that 50-60% of patients continue to experience symptoms in adulthood. When considering pediatric and adult cases, it is estimated that the prevalence of atopic dermatitis in the U.S. is 15 million. There is a relatively equal distribution of atopic dermatitis among males and females and there are no major differences in racial incidence.

Expenditures on the treatment of atopic dermatitis in the U.S. have been reported to exceed \$300 million per year. However, this figure may not reflect the intangible costs related to additional child care needs and missed days of work or school, particularly in light of the relatively high rates of either a personal or family history of asthma and allergic rhinitis in this patient population.

Interestingly, there is significant geographic variability in the prevalence of atopic dermatitis. For example, Asian countries report very low rates of atopic dermatitis, whereas countries such as the U.S., Great Britain, and Australia have much higher rates. In addition, there is a higher incidence of atopic dermatitis in inner city populations and individuals who live in dry climates. These findings support a possible role for environmental triggers in the initiation and exacerbation of disease.

Etiology, Pathogenesis, and Pathology

Although the exact cause of atopic dermatitis is not known, there is strong evidence for the contribution of both genetic and environmental factors in the pathogenesis of the disease. Most hypotheses suggest an immune-mediated mechanism in the development of atopic dermatitis. Patients may have a genetic predisposition to immune cell dysfunction in the skin. Subsequent exposure to environmental triggers, which may include allergens, such as pollens or dust mites, chemicals, and food components, results in abnormal activity of mast cells, basophils, eosinophils, and T lymphocytes in the skin. Mast cells and other degranulating cells localized to the skin become hypersensitive to stimuli and when activated release exaggerated amounts of inflammatory mediators, including histamine and leukotrienes, which are known for the ability to cause the classic redness, edema, and pruritis associated with dermatitis. In addition, T lymphocytes are thought to become chronically stimulated, which drives chronic immunological abnormalities in the skin.

The pathological hallmark of atopic dermatitis, as well as many other forms of eczematous dermatitis, is spongiosis of the epidermis of the skin, which involves the accumulation of edematous fluid between epidermal cells. The fluid forces an abnormal separation of epidermal cells that eventually leads to the development of the characteristic fluid-filled vesicles that accompany the dermatitis in these patients. The spongiosis also impairs the barrier function of the skin.

The genetic, allergic, and immune features that underlie the pathogenesis and pathophysiology of atopic dermatitis, particularly the allergen hypersensitivity, support the atopic nature of this skin disorder (atopy refers to a hereditary allergic mechanism). In addition, these mechanisms are consistent with the common finding of co-existing asthma and allergic rhinitis. However, the molecular genetic and environmental contributions to the pathogenesis of atopic dermatitis are not completely understood given that a significant fraction of patients do not exhibit allergen hypersensitivity and not all patients have a personal or family history of asthma or allergic rhinitis.

Clinical Features of Atopic Dermatitis

The classic clinical manifestation of atopic dermatitis is severe pruritis. Dermatitis is a major associated feature, which involves the development of a rash characterized by erythematous papules and vesicles. The most common sites of dermatitis and pruritis include skin creases, such as behind the knee, the crease at the elbow, and the neck, as well as the face, particularly the forehead, scalp, cheeks, and chin. Facial involvement is very common in infants and toddlers. In addition to dermatitis and pruritis, many patients present with evidence of persistent dry skin (xerosis), which can exacerbate the dermatitis.

The pruritis commonly provokes intense scratching by the patient, which can cause thickening and plaque formation (lichenification) and skin breakdown (excoriation). Given that the barrier properties of the skin are already compromised in atopic dermatitis, the additional pathological changes induced by chronic scratching can lead to secondary infections of the skin.

Although there are no consistent dermatological tests that readily differentiate atopic dermatitis from other types of eczematous dermatitis, a diagnosis of atopic dermatitis is strongly suggested by an infant or young child presenting with persistent pruritis and dermatitis and a personal or family history of asthma or allergic rhinitis. The most common clinical features of atopic dermatitis are summarized in Table 1.

The clinical course of atopic dermatitis is commonly described as relapsing and remitting. Flare-ups of symptoms may reflect increased or renewed exposure to environmental triggers. Atopic dermatitis can significantly impair the quality of life of patients and their families.

Drug Treatment of Atopic Dermatitis

Topical corticosteroids

According to the American Academy of Dermatology, topical corticosteroids are the standard of care in the treatment of moderate-to-severe atopic dermatitis. Results from a number of controlled clinical trials have established the efficacy and safety of these anti-inflammatory agents in the management of atopic dermatitis in infants and children, as well as in adult patients.

Topical corticosteroids are classified into six groups based on relative potency, which is derived from activity in a vasoconstriction assay and/or effectiveness in psoriasis. Potency can depend on the individual drug compound or the delivery vehicle. For example, betamethasone dipropionate cream and ointment are considered to be more potent than betamethasone dipropionate lotion. Group I and II agents are considered to be most potent, group III and IV products are of medium potency, and groups V and VI are lower potency (Table 2). It is recommended that lower potency topical corticosteroids be used in infants and young children, particularly if the skin of the face or intertriginous areas (e.g. skin folds of the groin and axilla) are to be treated. Medium potency agents may be used in older children and adults with more severe disease. In general, the highest potency corticosteroids are only indicated for patients 12 years of age and older with advanced lesions of atopic dermatitis localized to less delicate skin areas (e.g. lichenification and thick plaques on the palms of the hands).

Several treatment regimens have emerged from clinical trials. In the management of new onset moderate-to-severe atopic dermatitis or relapse of disease, a typical prescription will involve daily application of a low-to-medium potency topical corticosteroid preparation to affected areas for about one week. Once-daily application appears to be just as effective as 2 to 3 applications per day.

Historically, flare-ups of atopic dermatitis have been treated with short-term “bursts” of a topical corticosteroid until control of symptoms is achieved. Recently, however, studies have indicated that after management of the flare-up, a twice weekly maintenance application of a topical corticosteroid is effective and safe in increasing periods of remission and decreasing the risk of relapse. This treatment regimen is sometimes identified as *intermittent therapy* in the clinical literature.

Topical Corticosteroids: Adverse effects and Patient Information

Short-term topical corticosteroid therapy is generally well tolerated. One of the most common complaints is burning and stinging at the site of application that is reversible upon discontinuation of the medication. Potentially serious dermatological effects may include irreversible thinning of the epidermis, atrophy of the skin, telangiectasia (small, red-purple, dilated vessels in the skin), purpura (small hemorrhages in the skin), and striae (stretch marks). Findings from clinical trials demonstrate that the rates of these dermatological adverse effects are very low and the greatest risk results from inappropriate use of topical corticosteroids, particularly long-term, frequent application of high potency products. In order to minimize the possibility of adverse effects, healthcare professionals should exercise caution by using the least potent topical corticosteroid for the shortest possible time, particularly in infants and small children.

Although a major potential adverse effect of long-term and/or high-dose *systemic* corticosteroid therapy is suppression of the

adrenal axis and adrenal atrophy, this complication is relatively uncommon in topical corticosteroid treatment. Once again, the patients most at risk for significant systemic corticosteroid absorption and adrenal suppression are those receiving long-term, high potency topical corticosteroids, particularly infants and young children. This is a major reason why high potency products are not recommended in infants and young children. Except for recalcitrant, severe disease, most atopic dermatitis patients will respond favorably to short-term treatment with low-to-medium potency topical corticosteroids and thus be at minimal risk for adrenal axis suppression. Clinical trials have also demonstrated that adrenal axis suppression is highly unusual during the course of longer-term, twice-weekly intermittent/maintenance treatment of atopic dermatitis. A related concern regarding corticosteroids is growth inhibition in infants and children. Studies in children indicate that the appropriate use of low-to-medium potency topical corticosteroids does not significantly impact indicators of growth.

The patient or caregiver's understanding of the appropriate use of a topical corticosteroid product is a critical requirement for successful treatment with minimal adverse effects. The patient or family should be cautioned to use the topical corticosteroid only as directed by the physician. It is important to apply only a thin film of ointment, cream, or lotion and application should be restricted to affected areas of the skin. Although mild, temporary, burning or irritation may be expected, persistent, bothersome burning or stinging should be reported to the physician or pharmacists immediately. One potential patient or family question for the pharmacist is whether a dressing should be applied over the topical corticosteroid. Unless the physician specifically recommends or instructs the patient or caregiver in the use of an occlusive dressing, it should generally be avoided. Manufacturers of higher potency products caution against the use of dressings due to increased risk of enhanced systemic absorption of the corticosteroid. A similar complication can result from topical corticosteroids, particularly high potency products, applied on infant skin areas that come in contact with diapers.

Topical Calcineurin Inhibitors: Pimecrolimus and Tacrolimus

Pimecrolimus and tacrolimus are potent immunosuppressant agents that suppress T lymphocyte activation and inhibit the transcription of genes that code for a number inflammatory cytokines. Pimecrolimus and tacrolimus specifically inhibit the activity of calcineurin, a calcium-dependent phosphatase involved with signaling in T lymphocytes.

Although tacrolimus is available in an oral formulation for transplant rejection and treatment of severe Crohn's disease, the topical formulations of pimecrolimus (Elidel) and tacrolimus (Protopic) (Table 3) are indicated for atopic dermatitis only. More specifically, the prescribing information for Elidel and Protopic indicate that these products are *second-line* therapies for the short-term and *non-continuous* treatment of atopic dermatitis in non-

immunocompromised children age 2 or older and adults who have not adequately responded to topical corticosteroids. In contrast to topical corticosteroids, topical calcineurin inhibitors are not approved for use in infants.

Two randomized, vehicle-controlled, clinical trials with pimecrolimus cream, applied twice daily in children and adolescents age 2 to 17 for 6 weeks, demonstrated significant relief of signs and symptoms of atopic dermatitis, particularly pruritis. In addition, the extent of body involvement was also substantially decreased. Combined results from the two trials indicated that 35% of patients were found to be clear or almost clear of atopic dermatitis signs and symptoms after treatment with pimecrolimus cream. Most patients experienced significant improvement within 8 to 15 days of treatment.

Studies with tacrolimus ointment in both children and adults have produced similar results. Twice daily application of tacrolimus ointment over a 12 week period resulted in improvement in atopic dermatitis symptoms and a reduction in body surface involvement. Significantly more tacrolimus patients reported at least a 90% reduction in symptoms, based on a physician's global assessment of clinical response scale, compared to patients treated with vehicle alone. Most patients experienced significant improvement within 1 week of treatment. In addition, the trials revealed that 0.1% tacrolimus ointment may have better efficacy in the treatment of adults with severe atopic dermatitis and extensive body surface area involvement than the 0.03% ointment.

Pimecrolimus and tacrolimus: Adverse effects and Patient Information

Transient warmth, burning, and irritation after application are common complaints upon initiation of topical pimecrolimus and tacrolimus therapy. These effects usually diminish within the first week of treatment, which appears to correlate with improvement in atopic dermatitis lesions. The warmth, burning, and irritation do not necessitate discontinuation unless the effects become persistent and severe.

A potential complication with topical pimecrolimus and tacrolimus is increased risk of infection. The manufacturer emphasizes that these agents should never be applied if there is an active infection at the skin site. There is evidence that use of these agents may increase risk of varicella or herpes simplex infections. Likewise, these agents are contraindicated in immunocompromised patients.

A major concern with topical pimecrolimus and tacrolimus is a possible increase in the risk of carcinogenicity, particularly lymphomas and skin malignancies, which has prompted the FDA to advise the manufacturers of these products to include a black box warning in the prescribing information. The concern regarding malignancy is derived from clinical experience with systemic calcineurin inhibitors in transplant recipients, animal studies, and rare case reports of skin malignancies and lymphoma in patients treated with topical calcineurin inhibitors. Apparently the risk is most closely linked to long-term and/or high intensity immunosuppression

with these agents. Thus, the black box warning emphasizes that topical pimecrolimus and tacrolimus are not to be used in a long-term, continuous manner and that the safety of intermittent use beyond one year has not been established.

The manufacturers of these products encourage the use of readily available patient information sheets in order to reiterate the importance of only using a small amount of drug for each application and to limit application to affected areas of the skin. Patients are advised to notify their physician if there is no improvement or worsening of atopic dermatitis symptoms after 6 weeks of therapy or if there is any suspicion of a skin infection. Patients should also avoid the use of occlusive dressings with these products. Although there is no evidence that topical calcineurins are photosensitizing, patients should generally avoid prolonged exposure to treated skin areas. Both Elidel cream and Protopic ointment are supported by manufacturer-sponsored web sites that provide information for health care professionals and patients.

Emollients

The American Academy of Dermatology considers emollients to be a standard component of the preventative and maintenance care of atopic dermatitis. Emollients not only help relieve the severe dry skin often observed in atopic dermatitis, but there is evidence that effective moisturizing may enhance the patient's response to topical corticosteroid therapy. Emollients are highly recommended for application after the patient has bathed and dried affected areas of the skin.

Additional Pharmacological Treatments for Atopic Dermatitis

Topical corticosteroids, topical calcineurin inhibitors, and emollients are the principle pharmacological agents used in the treatment of atopic dermatitis. However, there are additional drug classes that have been studied for potential usefulness in atopic dermatitis patients.

Oral immunosuppressants and oral corticosteroids have demonstrated efficacy in severe atopic dermatitis, however the therapeutic benefit of these potent agents is outweighed by an unfavorable adverse effect profile. Topical coal tar is also effective, but there appears to be no advantage over topical corticosteroids and patient compliance is often hampered by problems such as odor and staining. Oral antihistamines do not have any direct clinical benefit in atopic dermatitis, although these agents may be useful in patients with co-existing allergic rhinitis. Finally, given that leukotrienes have been implicated in the pathophysiology of atopic dermatitis, it has been postulated that leukotriene inhibitor agents, such as montelukast, may be useful. Although a few small studies have demonstrated positive benefits, particularly in respect to diminishing the need for topical corticosteroids, a full understanding of the potential therapeutic utility of leukotriene inhibitors in atopic dermatitis will require larger studies.

Non-drug and alternative treatments

Allergen avoidance

Given the postulated role of allergen hypersensitivity in the pathogenesis of atopic dermatitis, it would appear that allergen identification and avoidance are important components of the management of atopic dermatitis. However, the medical literature does not provide clear evidence for the efficacy of allergen avoidance in the atopic dermatitis patient. Although studies focusing on strategies such as dietary restriction and dust mite reduction have demonstrated some benefit in patients that have specific hypersensitivities, there appears to be little or no direct benefit to the patient's atopic dermatitis. Some experts are concerned that parents of infants and children with atopic dermatitis often become overly concerned with identifying food and other allergies, which may actually impair compliance and the long-term success of treatment.

Ultraviolet phototherapy

Similar to the treatment of psoriasis, exposure of atopic dermatitis lesions to ultraviolet light has been shown to significantly reduce the severity of the patient's dermatitis and decrease the need for topical corticosteroids. A number of regimens have been studied, including psoralen (a photosensitizing agent) in combination with ultraviolet A light (PUVA) and combination ultraviolet A and ultraviolet B (UVA/UVB).

Dietary supplements

There is currently a tremendous interest in the potential role of dietary supplements in the prevention and treatment of disease. In respect to atopic dermatitis, a number of small trials and anecdotal reports have been published evaluating the potential usefulness of dietary supplements, including probiotics, such as lactobacilli, borage oil, evening primrose oil, zinc, and vitamin E. These studies have not demonstrated a clear therapeutic benefit in atopic dermatitis.

Role of The Pharmacist

As a drug information expert, the pharmacist can facilitate the successful treatment of the atopic dermatitis patient. By providing practical advice concerning the appropriate use of drug products, such as topical corticosteroids and calcineurin inhibitors, compliance can be optimized and adverse effects minimized. In addition, the pharmacist can diminish the stress and anxiety often experienced by patients and caregivers, particularly parents of infants and children with atopic dermatitis. The pharmacist may be one of the most accessible information resources for the latest developments in the treatment of atopic dermatitis, including alternative approaches.

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Table 1
Major Clinical Features of Atopic Dermatitis

Pruritis	A major criteria for the diagnosis of atopic dermatitis; most patients have a history of scratching, which can exacerbate the pathology and impair quality of life
Dermatitis	Characterized by a chronic or relapsing erythematous, vesicular rash, which can undergo lichenification and excoriation; common sites include skin creases, such as behind the knee, the crease at the elbow, and the neck, the limbs, and the face, particularly the forehead, scalp, cheeks, and chin
Dry skin (xerosis)	Chronically severe dry skin can further impair the barrier function of the skin and promote skin breakdown
Asthma or allergic rhinitis (hayfever)	70% of patients may have a family history of asthma or allergic rhinitis; 50% or more have a personal history of asthma or allergic rhinitis
Early age of onset	65% of patients are diagnosed in the first year of life and 90% by age five

Table 2
Classification of Topical Corticosteroids

Group	Selected Examples
Group I (very high potency)	Betamethasone dipropionate 0.05% cream or ointment in optimized vehicle (Diprolene) Betamethasone dipropionate 0.05% cream (Diprolene AF)
Group II (high potency)	Betamethasone dipropionate 0.05% ointment (Diprosone) Fluocinonide 0.05% cream or ointment (Lidex)
Group III (medium high potency)	Mometasone furoate 0.1% ointment (Elocon) Triamcinolone acetonide 0.5% cream (Aristocort)
Group IV (medium potency)	Fluocinolone acetonide 0.2% cream (Synalar HP) Triamcinolone acetonide 0.1% ointment (Aristocort)
Group V (lower potency)	Betamethasone valerate 0.1% cream or lotion (Valisone) Fluocinolone acetonide 0.025% cream (Synalar)
Group VI (low potency)	Aclometasone dipropionate 0.05% cream or ointment (Aclovate) Desonide 0.05% cream (Tridesilon)

Table 3
Topical Calcineurin Inhibitors

Drug Product	Recommended Dosage and Administration
Pimecrolimus 1% cream (Elidel) (available in 30, 60, and 100 gram tubes)	Children ages 2 to 15 years and adults: Apply a thin layer to affected areas of the skin twice daily
Tacrolimus 0.03% and 0.1% ointment (Protopic) (available in 30, 60, and 100 gram tubes)	Children ages 2 to 15 years: Apply a thin layer of the 0.03% ointment to affected areas of the skin twice daily Adults: Apply a thin layer of the 0.03% or 0.1% ointment to affected areas of the skin twice daily