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Clinical Evidence. Practical Advice

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A New Paradigm Shift in the Management of Atopic Dermatitis

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Introduction

Atopic eczema (or atopic dermatitis) is a common inflammatory skin condition that dermatologists, pediatricians, family physicians, and primary-care providers see on a daily basis. It generally presents as a chronically relapsing, highly pruritic, inflammatory skin disease that is associated with significantly reduced quality of life for patients and their families. Irritability, fatigue, sleep disturbances, treatment dependence, mood changes, and other psychological sequelae are frequently reported. Also, the social stigma associated with this visible skin condition should not be neglected.[1-3]

Overview of Atopic Dermatitis

- Eczema is characterized by a chronic course of recurring flares, as it often presents with periods of remission and flare-ups; continuous treatment and skin care are necessary.[1-3]
- Eczema can occur at any age, but it typically appears in early childhood (although late-onset disease is possible), with disease flares occurring periodically throughout the patient's life.[1]
- It is estimated that up to 17% of Canadians will develop atopic eczema at some point during their lifetime.[4]
- Atopic eczema has become more prevalent over the past few decades. Approximately half of eczema patients will develop the disease before 1 year of age.[2] Of these, approximately one-third will continue to suffer from eczema in adulthood.
- Most patients (approximately 85%) have mild to moderate disease.[1]

Pathogenic and Other Contributing Factors

- The exact cause of atopic eczema is unknown, however, it is believed to have a multifactorial pathogenesis, with genetics, impaired immune responses, the environment, and skin barrier defects being the most predominant contributing factors.[3]
- The epidermis is the body's first line of defense against environmental insults, as it forms a protective layer between the body and exogenous factors.[5]
  - An intact epidermal layer is essential for the skin to function as a physical and chemical barrier against environmental agents.[5]
  - Any breakdown in the epidermis increases skin moisture loss and the penetration of infectious and noxious external agents.[5]
- Several genetic factors are known to contribute to the dysfunction of the epidermal barrier in atopic eczema.
  - In particular, genetic defects associated with increased IgE (antibody) production and protease expression, and decreased levels of structural proteins in the epidermis have been linked to atopic eczema.
  - Gene mutations are believed to engender some of the aforementioned structural abnormalities in the epidermis and induce immune dysregulation.[4]

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- The scratching that can result from symptomatic pruritus may additionally cause skin trauma and excoriation, potentially leading to further inflammation, disease exacerbation, and secondary infections.
- Environmental factors may also contribute to skin barrier dysfunction, including washing with harsh soaps and detergents, and exposure to various infectious and noxious agents.
  - Soap or detergent use is one of the most common triggers of atopic eczema flares by adversely affecting the skin barrier. The use of inappropriate cleansing agents increases transepidermal water loss (TEWL), induces the release of pro-inflammatory cytokines, and elevates skin pH - provoking scaling, dryness, tightness and roughness, erythema, and swelling.

Treatment Rationale

Management of atopic dermatitis is frequently multimodal, incorporating several non-pharmacologic and pharmacologic approaches.

- Basic skin care practices, such as quick daily bathing and gentle cleansing of skin with mild, unscented soaps/cleansers, followed by moisturization (hydration) with emollients can minimize the skin impairment and treat the symptoms of dry skin and itching.[6]
- Additionally, the avoidance of irritants and other triggers known to exacerbate atopic eczema may prove useful in preventing flares.[6]
- However, despite vigilant skin care practices, most patients will continue to experience atopic eczema symptoms and recurrent flares that will require pharmacologic treatment.[6]

Treatment Options (Table 1)

Topical Corticosteroids

- Topical corticosteroids have been the predominant atopic eczema therapy for more than four decades - they provide flare control through their anti-inflammatory, anti-proliferative, immunosuppressive, and vasoconstrictive actions.
- Common adverse effects of topical corticosteriods include striation, skin thinning and atrophy, and potential systemic effects.[3]

Topical Calcineurin Inhibitors

- The topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, are alternative topical anti-inflammatory agents in the clinician's armamentarium.
- These agents may be used on all body parts, including sensitive areas, such as the face, neck, and groin.
- They can also be used in patients who have experienced steroid related side-effects or in those suffering from a chronic disease that is unresponsive to topical steroids, as well as in patients for whom therapy with steroids is inadvisable or has been unsuccessful.[2]
- The calcineurin inhibitors do not cause the adverse effects on collagen synthesis or skin thickness as compared with topical corticosteroids.[7]
- Long-term treatment with tacrolimus has also been associated with improvements in collagen synthesis and skin thickness.[7]

Antimicrobials

- Antimicrobials are commonly prescribed for clinically infected eczematous lesions where *Staphylococcus aureus* colonization is suspected as a contributing factor.
- Short-term combination topical therapy with an antibiotic and corticosteroid is widely used. However, overuse and prolonged treatment increases the risk for developing antibiotic resistance.
- A recent report in *Cochrane Database Systematic Review* did not find clear evidence of benefit for antimicrobial interventions in atopic dermatitis patients.[8]

Lifestyle/Non-pharmacologic Strategies

- Identify and eliminate triggering factors
- Avoid allergens
  - Environmental (e.g., house dust, dust mites, pollens, animal dander, moulds, smoke)
  - Food (e.g., milk, egg whites, peanuts, soybeans, tree nuts, fish, shellfish, wheat)
- Minimize exposure to irritants (e.g., wool, perfumes, soap, hot baths or showers)
- Use emollients to hydrate and rehydrate
- Ensure that sports equipment is dried completely - sweat is a common irritant
- Encourage patient self-education, suggest visiting reputable websites (e.g., Canadian Skin Patient Alliance, Eczema Society of Canada, and the Canadian Dermatology Association)

Clear	Mild	Moderate	Severe
• Emollients	• Emollients	• Emollients	• Emollients
	• Topical calcineurin inhibitors	• Topical calcineurin inhibitors	• Topical calcineurin inhibitors
	• Mild topical corticosteroids	• Moderate topical corticosteroids	• Potent topical corticosteroids
			• Systemic therapy • Phototherapy

+/– topical or systemic antimicrobials based on patient-specific clinical assessment

Table 1: Overview of pharmacologic treatment strategies for atopic eczema

A Paradigm Shift in the Management of Eczema

- Conventional therapeutic approaches have been recently challenged by a newer strategy that takes a preventative long-term approach to treating atopic eczema.[7,9]
- The clinical justification for preventative maintenance therapy is that it can improve atopic eczema related skin barrier dysfunction and diminish the immunological inflammatory abnormalities often associated with chronic eczematous flares and disease exacerbation.[9]
- The preventative maintenance approach uses intensive topical anti-inflammatory therapy until visible lesions have nearly cleared.[7,9] This is followed by low dose intermittent application, usually twice weekly, of anti-inflammatory agents to previously affected skin areas to prevent flares and disease exacerbation.[7,9]
- Several clinical trials comparing the preventative to the traditional "reactive" approach using topical corticosteroids have shown that preventative therapy is an effective strategy.[10]
- In 2002, Hanifin et al. published a randomized, double-blinded, 20-week clinical trial comparing the preventative application of 0.05% fluticasone cream with vehicle cream.[11]
  - Patients preventatively receiving 0.05% fluticasone cream were 7.7 times less likely to experience a flare relapse than those receiving vehicle.
- Alternatively, preventative use of 0.1 % and 0.03% tacrolimus ointment was recently studied in two large, multicentre, randomized, double-blind, 12-month clinical trials involving adult (n=257) and pediatric (n=125) atopic eczema patients.[9]
  - Patients were randomized to twice-weekly preventative tacrolimus therapy or twice-weekly vehicle after an initial flare treatment with twice-daily tacrolimus ointment.
  - Preventative application of tacrolimus significantly reduced the number of disease exacerbations requiring substantial therapeutic intervention in both treatment populations.
  - Preventative therapy also resulted in significantly fewer treatment days (12.4 vs. 31.5), and increased flare-free time until first relapse (142 days vs. 15 days) in adult patients.[9-14] In addition, preventative therapy in children significantly reduced the number of treatment days (34.0 vs. 59.9), and prolonged the time to first relapse compared with reactive treatment (295 days vs. 56 days).[12-15]
  - Similar results have also been shown in trials reporting the use of pimecrolimus cream for flare prevention in children.[13]
- TCIs may offer benefits over corticosteroids in the long-term treatment of atopic eczema given their lack of association with skin atrophy and decrease in collagen synthesis.[3-7,9]
- Based on the above studies, in September 2010, Health Canada approved a new indication for the use of tacrolimus ointment as maintenance therapy in moderate to severe atopic dermatitis.[16]

Conclusion

As there is no cure for atopic eczema, a long-term strategy for disease control and management is of significant importance for this chronically relapsing condition. Recent insights into the mechanisms that drive cutaneous inflammation have led to a better understanding of atopic eczema and highlighted the role of the epidermal barrier in its pathogenesis. Targeting the skin barrier and restoring its function may prove an effective treatment strategy for atopic eczema. Preventative treatment with topical steroids and TCIs offer a novel therapeutic approach with clinical implications for physicians and their patients. Furthermore, studies have shown that topical tacrolimus may confer additional benefits, as it improves the functionality of the skin barrier and does not cause skin atrophy. As demonstrated in clinical investigations, the substantial reduction in flare-ups among preventatively treated patients may result in fewer atopic eczema-related physician visits and quality of life improvements (e.g., work/school performance).

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Topical Approaches in Combination Therapy for Acne

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Introduction

Acne vulgaris is a common chronic inflammatory cutaneous disease involving the pilosebaceous unit. Its pathophysiology is multifactorial and complex, including obstruction of the pilosebaceous unit due to increased sebum production, abnormal keratinization, proliferation of *Propionibacterium acnes* (*P. acnes*), and inflammation.

Topical agents are the most commonly used therapy for acne. First generation topicals mainly consist of single agent retinoids, benzoyl peroxide (BP), and antibacterials that target comedones, *P. acnes*, and inflammation. Novel topical therapies include combination products with advanced vehicle formulations that target multiple acne pathophysiologies and offer simplified treatment regimes. For example, the combination of clindamycin and tretinoin in a unique vehicle formulation of suspended crystalline tretinoin allows for progressive follicle penetration and decreased irritation, resulting in increased efficacy. Furthermore, adapalene or clindamycin with BP combinations target comedones, inflammation, and *P. acnes* synergistically. These newer combination products have the potential to increase both efficacy and patient adherence when compared with single agent treatment.

Disease Overview

Diagnostic Features and Grading (Table 1)

- Acne vulgaris has distinguishing comedones (open and closed) and inflammatory lesions in the form of papules, pustules, or nodules and cysts.[1,2]
- The presence of comedones confirms the diagnosis of acne vulgaris.[3]

Severity	Grade	Description
Mild	I	Open and closed comedones and few inflammatory lesions
Mild to moderate	II	Comedones with occasional inflammatory papules and pustules that are confined to the face
Moderate to severe	III	Many comedones with small and large inflammatory papules and pustules; more extensive but confined to the face
Severe	IV	Many comedones and inflammatory lesions with nodules and cysts tending to coalesce and canalize; involving the face and the upper aspects of the trunk

Table 1: Severity grading of acne vulgaris[2,3]

Differential Diagnosis Include:

- Rosacea
- Perioral dermatitis
- Bacterial folliculitis
- Drug induced acneiform eruptions

Prevalence, Pathophysiology and Psychosocial Impacts

- Acne is a common worldwide skin disease that affects about 85% of individuals between the ages of 12-24 years.[4]
- The four main pathophysiologic features include: [3]
  1. androgen-mediated stimulation of sebaceous gland activity,
  2. abnormal keratinization leading to follicular plugging (comedone formation),
  3. proliferation of *P. acnes* within the follicle, and
  4. inflammation.
- Genetic factors, stress, and possibly diet may influence the development of acne.[3]
- Acne can cause a considerable amount of emotional distress and physical discomfort, thus, medical treatment must be accompanied by patient counseling and education, which can contribute to improved self-esteem and adherence to therapy.

Topical Treatment Overview and Options

Topical therapy (Tables 2 and 3) is used for mild to moderate acne and also for maintenance therapy in all levels of disease severity.

Acne Severity	Treatment
Mild	• Topical retinoids for treatment and maintenance
Mild to moderate	• Benzoyl peroxide + topical antibiotics +/– topical retinoids; 8 to 12 week course
Moderate to severe	• Topical therapies used in mild to moderate acne + oral antibiotics for a minimum of 6 to 8 weeks
Severe	• Oral isotretinoin; 16 to 20 week course

Table 2: Treatment indications based on acne severity[3-5]

Drug Type	Topical Acne Agents	Overview
Retinoids	• Adapalene • Tazarotene • Tretinoin	• Effective against acne vulgaris through comedolysis, which acts to reduce dyskeratosis at the pilosebaceous unit • Inhibits the formation of microcomedones and has mild anti-inflammatory effects[6] • Gel, cream, and solution formulations may induce irritation and dryness • Advanced formulations include an emollient cream and microsphere gel • Vehicle delivery advancements reduce irritation and enhance efficacy
Antimicrobials	• Benzoyl peroxide • Clindamycin • Erythromycin • Sodium sulfacetamide	• Bactericidal or bacteriostatic action directed against *P. acnes* • Formulated in creams, lotions, and gels • Can induce irritation and dryness • Benzoyl peroxide may bleach coloured fabrics • Antibiotics have anti-inflammatory properties
Combination products	• Benzoyl peroxide + antibiotic • Retinoid + antibiotic	• Facilitates treatment of multiple pathogenic factors that are complementary and synergistic in mechanisms of action • Combined efficacy is greater than either agent alone[6] • Gel formulations • Simplifies treatment regimen and reduces dosing frequency • Combined use of benzoyl peroxide + topical antibiotic can reduce bacterial resistance; once opened, these products have a limited shelf life (3 to 4 months)

Table 3: Topical therapies currently used for acne vulgaris treatment[5]

Newer Novel Topical Agents

Clindamycin Phosphate 1.2% + Tretinoin 0.025% Gel

- This fixed-dose combination gel was approved by Health Canada in December 2010 and is indicated for mild to moderate comedonal and inflammatory acne vulgaris in patients ≥12 years of age.[7]
- It combines the anti-inflammatory and antibacterial actions of clindamycin with the comedolytic and anticomedogenic actions of tretinoin[7] to target several mechanisms in the pathogenesis of acne.
- Multiple studies have demonstrated significantly greater reductions in comedones and inflammatory lesions by 12 weeks compared with either agent alone or vehicle.[8-10]
- A more rapid reduction in acne lesions was observed by 8 weeks compared with either agent alone or vehicle.[8]
- Application is recommended once-daily at bedtime (preferred) or morning (as the vehicle delivery formulation provides for the photostability of tretinoin).[7]
  - Patients should be instructed to use only a pea-sized amount.
- Vehicle characteristics
  - It is available as an aqueous gel that is alcohol free with a unique formulation.[11]
  - It contains solubilized clindamycin phosphate and a stable combination of both solubilized and crystalline tretinoin.[11]

- The crystalline suspension allows for tretinoin to be released in a rate-controlled manner, thereby resulting in slower and progressive follicular penetration and increased tolerability.[11]
- Long-term efficacy and a favourable safety profile was shown in a 52 week study.[12]

- Side-effects and contraindications
  - Crohn's disease, ulcerative colitis, colitis with previous antibiotic therapy, use of concomitant erythromycin-containing products, pregnancy (category C)[7]
  - Side-effects from topical retinoids may include peeling, redness, dryness, itching, and photosensitivity.
  - Because tretinoin increases the skin's sensitivity to UV light, patients should be reminded to avoid excessive or unnecessary sun exposure and wear sunscreen and protective clothing daily.

Adapalene 0.1% + BP 2.5% Gel

- This combination treatment was US FDA approved in January 2009 and is currently under review by Health Canada.
- Proposed mechanism of action: adapalene has comedolytic, anticomedogenic, and anti-inflammatory effects and BP is a highly lipophilic oxidizing agent with bacteriocidal and keratolytic effects.[13]
- BP lowers the incidence of bacterial resistance compared with other topical antibiotics and can be used for the long-term management of acne.
- The complementary modes of action address 3 out of the 4 pathophysiologic processes of acne:
  1. abnormal keratinization leading to follicular plugging (comedone formation),
  2. proliferation of the bacterium *P. acnes* within the follicle, and
  3. inflammation.
- Large double-blinded randomized controlled trials showed that this combination gel was significantly more effective than the respective monotherapies, producing marked differences in total lesion counts.[14,15]
- Studies demonstrated a comparable safety profile to adapalene.[15]
- Adapalene is stable when combined with BP in the presence or absence of light.[13]
- Once-daily dosing provides regime simplicity.

Patient Adherence

Acne is a chronic disease and poor medication adherence is a major contributor to treatment unresponsiveness.[16] Factors that can impact treatment follow-through include:

- Convenience and decreased complexity of treatment encourage patient adherence.
- Treatment regimens that are effective and well-tolerated, as well as simple and easy to incorporate into the patient's lifestyle, are more likely to increase adherence.
- Patients most commonly attribute frustration with the therapeutic regimen and forgetfulness as reasons for failure to use prescribed medications.[17]

Conclusion

The successful topical treatment of acne depends on appropriate agent selection based on patient-specific acne severity, tolerance, adherence, and adequate follow-up. The advent of combinational therapeutic products provide increased efficacy by targeting multiple pathophysiologic processes. Additional advantages of using combination therapy include reduced complexity of treatment regimen and convenient once-daily dosing. The future of topical acne treatment holds the promise of more novel uses of conventional anti-acne agents formulated with advanced vehicle delivery systems that offer less side-effects, increased tolerance, dosing simplicity, and improved efficacy.

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