Family Practice Edition

Skin Therapy Letter

Volume 7 • Number 5 • October 2011

Clinical Evidence. Practical Advice

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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 • Sulfonamides inhibit *P. acnes* with limited potential for antibiotic resistance
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 (Biacna™)

- This fixed-dose combination gel was approved by Health Canada in December 2010 for the topical treatment of 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% + Benzoyl Peroxide 2.5% Gel (Tactuo™)

- This combination treatment was Health Canada approved in May 2011.
- 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.

Bacterial Resistance in Acne

- Antibiotics are recommended for use with BP (available in gel, lotion, and wash).
- BP is an efficient bactericidal agent that will minimize the development of bacterial resistance at skin sites where topical antibiotic (i.e., clindamycin and erythromycin) therapy is applied.
- BP is effective against both nonresistant and resistant *P. acnes* strains.[16]
- A 4-week randomized study of patients with mild to moderate acne explored the safety and tolerability of fixed combination clindamycin phosphate and tretinoin gel (CT) once-daily in conjunction with morning use of a BP wash, targeting several pathologic factors and limiting the potential for clindamycin-induced *P. acnes* resistant strains.[17]
  - Side-effects were mild and included transient dryness, scaling, erythema, burning, stinging, and itching during the first week of therapy, then improving within 1-2 weeks.
  - CT gel + BP wash was shown to be a safe and well-tolerated therapeutic regimen to effectively treat acne while mitigating the potential for bacterial resistance.

Patient Adherence

Acne is a chronic disease and poor medication adherence is a major contributor to treatment unresponsiveness.[18] 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.[19]

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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Atopic Dermatitis: The Skin Barrier and the Role of Ceramides

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Introduction

- Atopic dermatitis (AD) or eczema is a chronic, inflammatory, pruritic skin condition of increasing prevalence that often precedes other atopic conditions such as asthma or allergic rhinitis.[1]
- The lifetime prevalence of AD is estimated at up to 17% of Canadians having been affected.[2]
- Atopic dermatitis may account for up to 30% of dermatologic consultations in general practice.[3]
- Most cases of AD start in children under 5 years of age. Although 60% of patients with childhood AD are estimated to be free of symptoms in adolescence, up to half may experience adulthood recurrence.[4]
- Multiple severity scales and diagnostic criteria for AD have been adopted, but Hanifin and Rajka's clinical criteria[5] has been widely accepted. AD diagnosis requires the presence of at least 3 of these major criteria :
  - Characteristic lesion distribution
  - Pruritus
  - Chronic progression with recurrences
  - Personal or family history of atopy (asthma, allergic rhinitis, AD)
- Three clinical stages usually characterize AD, depending on age group:[1]
  1. in infancy AD usually presents on cheeks and scalp,
  2. in childhood on the flexural areas, neck, and dorsal limbs, and
  3. in adolescence/adulthood lichenified plaques of the head, neck, and flexural areas.

Pathogenesis

Filaggrin Gene

- Loss of function mutations in the filaggrin gene (also found in icthyosis vulgaris), has been identified in patients with AD.[1] Filaggrin gene defects can also be associated with increased risk of allergic rhinitis and asthma in patients with eczema.[6]
- Filaggrin normally assists in cytoskeletal aggregation and formation of the cornified cell envelope functioning to prevent water loss, creating a barrier to external insults.
- There have been several potential genes identified in AD, for example those encoding cytokines involved in IgE synthesis regulation (IL-4, IL-5, IL-12, IL-13, and GM-CSF), and gene polymorphisms involved in innate immunity contributing to imbalance between Th1 and Th2 immune responses.[1]

Epidermal Barrier Dysfunction

- There is strong evidence to support that barrier abnormalities play a major role in disease pathogenesis, with recent focus on emollient and lipid replacement therapy to address barrier dysfunction and decrease inflammation.[7]
- The structure of the epidermal skin barrier, the stratum corneum, is commonly analogized to a "brick and mortar"[8] model. The "bricks" consist of a network of compact corneocyte multilayers and the intercellular lipid matrix (composed of ceramides, cholesterol, and free fatty acids) form the "mortar". These hydrophobic lipids function as water-retaining molecules, with their precursors secreted by the epidermal lamellar body that also deliver antimicrobial peptides and enzymes that assist in lipid generation and corneocyte shedding.[7]
- An intact stratum corneum functions to maintain skin hydration and protect against water loss.
- In AD, the pathogenic skin barrier is characterized by increased transepidermal water loss (TEWL), decreased water-binding properties, and reduced surface lipids, primarily ceramides.[9]

General Treatment Principles

- Avoidance of trigger factors and optimization of the skin barrier function with emollients/moisturizers are key elements at all stages of treatment in AD.
- Increasing severity of disease calls for the addition of multiple therapeutic agents in stepwise fashion.
- Current treatment options for AD target either restoration of skin barrier function, inflammation, and/or infection/microbial colonization.
- Production of antimicrobial peptides and molecular recognition of invading pathogens has been shown to be defective in AD.[10] Colonization of the skin with *Staphylococcus aureus* is frequently found in AD, which in combination with a disfunctional skin barrier can result in secondary infection requiring antimicrobials, such as impetiginization, folliculitis, and cellulitis or abscesses.[1]

Moisturizers

- Moisturization has been shown to improve skin barrier function in AD with faster resolution of symptoms,[11,12] and continual treatment appears to reduce re-exacerbation.[13]
- Controlled clinical studies have demonstrated that moisturizers enhance topical corticosteroid efficacy. Moisturizers are also shown to have a steroid-sparing effect.[9]

- Liberal use of emollients (cream or ointment) is suggested (e.g., 500 g every 1 to 2 weeks).[3]
- Some emollients (e.g., containing urea, lactic acid, or propylene glycol) can cause irritation and burning, and contact dermatitis may occur in susceptible patients to certain fragrances and preservatives.[14]
- A reduction in lipids, particularly ceramides, correlate positively with barrier impairment in AD. Use of lipid-containing moisturizers may be beneficial in promoting barrier recovery.[9,14]

Ceramides as Moisturizers

- Patients with AD produce fewer and different lipids, and have higher ceramide degradation,[10] leading to a selective reduction in the ceramide fraction.[12]
- Most current water-in-oil emollients/moisturizers do not address nor correct this underlying lipid abnormality.
- Topical mixtures containing ceramide, cholesterol, and free fatty acids have been shown to accelerate barrier repair.[11]
- Lipid-based barrier repair cream available in Canada include CeraVe® (available over-the-counter) and EpiCeram® (prescription only).
- Ceramide-containing creams, lotions and cleansers (e.g., CeraVe®) can be delivered through time-released multilamellar vesicular emulsions (MVE).
- Such MVEs deliver ceramides, cholesterol, free fatty acids, and other moisturizing ingredients (hyaluronic acid, glycerine and dimethicone) into the skin in a 24-hour controlled, time-released manner. This delivery advance offers once-daily application, thereby encouraging adherence to a simplified regimen of moisturizer use.
- The combination of MVEs with other topical treatments has recently been shown to accelerate skin barrier recovery.[15]
- More education for AD patients on the benefits of ceramide creams is needed, as the use of such preparations is associated with poor patient knowledge and compliance.[16]
- In addition to AD, ceramide-based moisturizers may have a role in managing other cutaneous disorders that cause or exacerbate skin barrier impairment, such as acne, psoriasis, and rosacea.
- The cost comparison of various barrier repair creams may bear an impact on therapeutic decision-making.

Topical Therapies

Corticosteroids and Calcineurin inhibitors

- Uninvolved skin of AD patients harbours subclinical inflammation.
- Proactive therapy, a recent therapeutic concept, aims at targeting subclinical inflammation before it flares into clinically relevant AD.
- There are two main topical modalities in anti-inflammatory treatment: corticosteroids and calcineurin inhibitors.
- With mild AD, small amounts of TCS in combination with emollients/moisturizers are sufficient to maintain an acceptable skin status without significant adverse effects.[10]
- Tapering of corticosteroids, in terms of progressive reduction in potency and reduction in application frequency, once the erythema has subsided is crucial.
- Topical calcineurin inhibitors (TCIs), such as topical tacrolimus or pimecrolimus, reduce proinflammatory cytokines by inhibiting the calcineurin-dependent pathway.
- Tacrolimus 0.1% ointment is similar to an intermediate potency corticosteroid and pimecrolimus 1.0% cream is slightly less potent.[10]
- TCIs do not cause skin atrophy, and thus, may be used on sensitive areas (e.g., face, eyelids, perioral region, genital area, axillary region, or inguinal folds).
- Health Canada has recently approved topical tacrolimus ointment twice-weekly for the prevention of eczema flares in those who experience a high frequency of flares (> 5 times per year) based on two Phase 3 multi-centre randomized clinical trials in pediatric and adult patients.[17,18]
  - Preventative therapy with tacrolimus has been shown to significantly reduce treatment days and prolong intervals between flares.[17,18] Similar findings have also been reported in the use of pimecrolimus cream for flare prevention in children.[19]

Systemic Therapy

- Numerous systemic treatments can be used in severe acute flare-ups of AD when topical therapy with immunomodulators fails to control the disease. These include phototherapy, methotrexate, azathioprine, and cyclosporine A.
- Antihistamines do not directly relieve pruritis; however, when taken before bed central sedative effects can discourage scratching and improve sleep quality.

Other Tips

Patient Education

- A survey[16] of 422 patients with chronic skin conditions and compromised skin barrier function revealed general underuse of moisturizers. The survey also emphasized that patient education is important in promoting compliance and clinicians should provide more information on the essential role of moisturizers and cleansers in skin barrier repair.
  - Cleansers containing ceramides and emollients can minimize any barrier disturbance by simultaneously replacing lipids that are lost during washing.
- Explaining the nature and course of atopic dermatitis, trigger avoidance and lifestyle changes, and therapeutic options, as well as demonstrating proper use of treatment are key to management. Supplemental educational brochures and a written plan of care that is reinforced at follow-up visits may also be helpful.[3]

Lifestyle Modifications

- Identify and avoid triggers
  - Common triggers or exacerbating factors include sweating, hot baths, stress, wool clothing, dry environments, harsh soaps, and detergents
- Avoid scratching
- Keep nails trimmed, wear gloves at night to avoid scratching and enhance penetration of topical therapies
- Cool wet compresses can provide temporary relief
- Wear cotton clothing

- Choose fragrance-free skin care products and laundry detergent
- Double rinse clothing
- Short (<15 minutes) lukewarm baths followed by moisturization
- Moisturize regularly

Conclusion

AD follows a chronic relapsing course. As such, in addition to pharmacologic intervention, it is essential to maintain hydration and barrier function of the skin with daily regimented moisturizer use. Ceramide-based moisturizers have been shown to be beneficial in reducing TEWL, improving barrier function, and maintaining hydration of the stratum corneum, and thus, can be a useful component in AD management. Adequate moisturization reduces the need for drug treatments, as well as limits the severity and frequency of eczematous flares.

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Topical Management of Recalcitrant Psoriasis and Eczema

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Reprinted from Skin Therapy Letter FP 6(3):1-4 (December 2010) due to content update

Introduction

Psoriasis and eczema, especially atopic eczema, are two of the most common cutaneous conditions seen by family physicians and dermatologists. Although the etiology of both conditions is unknown, immunologic abnormalities with an increase in immune mediators are thought to play major roles. These skin disorders are not curable, but can be controlled with proper topical therapy. However, psoriasis and eczema can at times be recalcitrant to conservative topical treatment. As such, it may be helpful for family physicians to be aware of more aggressive or innovative topical options for recalcitrant cases. Patients unresponsive to aggressive topical therapy may require systemic treatment or phototherapy, which carry a greater potential for adverse effects. Such cases are best managed by dermatologists with more experience in using these therapies.

Overview of Topical Corticosteroids

Due to their anti-inflammatory, immunosuppressive, and anti-proliferative properties, corticosteroids are effective for treating a variety of inflammatory dermatoses, including psoriasis and atopic eczema.

Potency

- The potency rating of a topical corticosteroid describes the intensity of the agent's clinical effect.[1] Seven groups of topical steroid potencies have been developed, these are ranked from superpotent (Group 1) to low potency (Group 7). Table 1 lists the topical corticosteroid potencies and gives available examples in Canada.

Vehicle Considerations

- Ointments are water-in-oil emulsions and are more hydrating to the stratum corneum. They provide an occlusive barrier, and because of an increased depot effect, drug penetration is enhanced, leading to greater potency.
  - For example, Table 1 shows the same chemical compound, triamcinolone acetonide 0.1%, can be Class 4 potency as an ointment, but only Class 5 as a cream. Therefore, an ointment can be useful in treating refractory dermatoses, especially for thick, fissured, and lichenified skin lesions.

Administration and Dosing

- Localized recalcitrant conditions may benefit from using a corticosteroid ointment under occlusion (e.g., plastic wraps and hydrocolloid dressings), which can increase the drug permeability up to 10 times.[2]
- Topical corticosteroids are usually applied once or twice daily. The duration of daily use of ultra-potent formulations should not exceed 3 weeks.[3] Medium and high strength topical corticosteroids can be used up to 3 months.[3] It can be difficult to adhere to these guidelines, as psoriasis and atopic eczema are chronic, requiring long-term therapy.
- In general, it is best to treat active disease more aggressively and then taper to the lowest strength that can maintain disease control.
- Use of superpotent topical corticosteroids should not exceed 50 grams per week in order to avoid excessive absorption and adrenal suppression.

Adverse Effects from Overuse or Prolonged Use

- Risks from long-term topical corticosteroid use include tachyphylaxis - a diminished pharmacologic response after repeated drug administration.[1]
- There is a potential for rebound - a severe exacerbation of the dermatosis after abrupt discontinuation.[4]
- Systemic complications include suppression of the hypothalamic-pituitary axis, hyperglycemia, Cushing's syndrome, and avascular necrosis.[4]
- Local adverse effects associated with prolonged use of potent topical corticosteroids include skin atrophy, striae, purpura, telangiectasia, acneiform eruptions (steroid-induced acne, perioral dermatitis, and rosacea), hypopigmentation, and hypertrichosis.[4]

Topical Treatment of Psoriasis Vulgaris

Psoriasis vulgaris is a common, chronic, inflammatory skin disease affecting 2% of the population.[5] Most psoriatic patients have limited disease (<5% body surface area) and can be successfully treated with topical agents.[5] Plaque psoriasis (PPs) and psoriasis involving the scalp, palms or soles can be particularly refractory to topical therapy.

Topical agents used to treat psoriasis include corticosteroids, vitamin D analogue (calcipotriol), retinoids (tazarotene), tar, anthralin,[6] salicylic acid, and topical calcineurin inhibitors (TCIs). Also, combination therapies are available and may be useful because of their increased potency, decreased side-effects, and increased adherence due to less frequent dosing. A systematic review of topical treatments for chronic PPs included 131 randomized controlled trials with 21,448 participants concluded:[7]

- Vitamin D analogue (calcipotriol) was significantly more effective than placebo.
- Potent (betamethasone dipropionate) and very potent (clobetasol propionate) topical corticosteroids were better than placebo, with very potent preparations working better than weaker ones.
- Dithranol (anthralin) and tazarotene worked better than placebo.

- Combination therapies with a vitamin D analogue (calcipotriol) and a potent corticosteroid were more effective than either product alone.
- Potent topical corticosteroids were less likely than calcipotriol to cause local adverse events.

Recalcitrant Plaque Psoriasis

For recalcitrant PPs, a well-tolerated first-line regime would normally be a combination of a vitamin D analogue (calcipotriol) and potent steroid (betamethasone dipropionate 0.05%) applied daily at bedtime.

- Resistant patients can also be treated with a potent corticosteroid, such as clobetasol propionate 0.05% cream or ointment, twice daily for 2-3 weeks.
  - Use of a potent corticosteroid as "intermittent pulse dosing" may be helpful as a maintenance regimen.[8]
  - In this regimen, after clearing the patient with the potent steroid, remission is maintained with continued use of the potent steroid, using it for 3 consecutive doses at 12-hour intervals once weekly.
  - A study using betamethasone dipropionate glycol 0.05% with this regimen extended remission to 6 months in 60% of patients.[9] No serious local or systemic side-effects were observed.
- A new treatment that may be effective for recalcitrant PPs of the body is clobetasol propionate 0.05% spray.
  - In a randomized double-blinded vehicle-controlled study of moderate to severe psoriasis, 75% of patients were reported to be clear or almost clear at 4 weeks following twice daily use of the spray.[10]
  - There were no reports of hypothalamic-pituitary-adrenal suppression and patients showed reductions in scaling, erythema, and plaque elevation.
- Calcipotriol + betamethasone dipropionate ointment, clobetasol propionate ointment, followed by pulsed therapy, or clobetasol propionate 0.05% spray could be tried for recalcitrant psoriasis on the palms and soles.
  - Very potent steroids can be used on the palms with little risk of atrophy. Superpotent steroids have been used under occlusion on palms and soles with good results.[11]
- Tazarotene cream or gel can be used as monotherapy, but this retinoid is often used in combination with a topical steroid, such as mometasone furoate 0.1% cream, to reduce skin irritation, which is the major side-effect of tazarotene.
  - Tazarotene 0.1% gel once daily in combination with mometasone furoate 0.1% cream once daily has been shown to be more effective than calcipotriol ointment twice daily or mometasone furoate 0.1% cream twice daily.[12]

Scalp Psoriasis

For recalcitrant scalp psoriasis, the following treatments could be considered:

- Salicylic acid 3% + betamethasone dipropionate 0.05% lotion may be helpful as the salicylic acid has been shown to increase penetration of the topical steroid.[13]
- A new gel formulation containing calcipotriol + betamethasone dipropionate 0.05 % can be very helpful for moderate to severe scalp psoriasis.[14]
- A clobetasol propionate 0.05% shampoo applied to the scalp for 15 minutes and then lathered and shampooed out can be effective for difficult scalp psoriasis.[15]
- Another option is fluocinolone 0.01% in a peanut oil base that is applied to the scalp under a shower cap at bedtime and washed out the next morning.

Topical Treatment Suggestions for Recalcitrant Psoriasis

Plaque Psoriasis (excluding face and body folds)

- Calcipotriol + betamethasone dipropionate ointment (e.g., Dovobet™)
- Pulsed superpotent topical corticosteroids, such as clobetasol propionate or halobetasol propionate 0.05% (e.g., Ultravate®) ointment/cream used twice daily Saturday and Sunday
- Clobetasol propionate spray (e.g., Clobex™)

Palms and Soles

- All treatments suggested for plaque psoriasis (above) can be tried
- Superpotent topical corticosteroid with saran wrap or hydrocolloid occlusion overnight
- Topical tazarotene 0.1% cream/gel once daily +/– topical mometasone furoate 0.1% cream once daily

Scalp Psoriasis

- Betamethasone dipropionate + salicylic acid lotion (e.g., Diprosalic™)
- Calcipotriol + betamethasone dipropionate (e.g., Xamiol™ gel)
- Clobetasol propionate shampoo (e.g., Clobex™)
- Fluocinolone acetonide topical oil 0.01% (e.g., Derma-Smoothe/FS®)

Dosing Strategies for Protracted Remission

- Typically, Class 1 topical steroids are prescribed for rapid clearing in acute flares. Following initial control of psoriasis with a superpotent topical steroid, weekend-only therapy has been demonstrated to be extremely beneficial in maintaining long-term remission.[16-19]
- With the aim of prolonging the initial therapeutic response while limiting the risks associated with extended corticosteroid use, a recent randomized, double-blind, placebo-controlled study of mild to moderate psoriasis assessed the safety and efficacy of a combination regimen of initial short course superpotent corticosteroid (halobetasol ointment 0.05%) followed by long-term weekend-only use to previously affected sites of psoriasis.[16] Twice daily adjunctive therapy with a moisturizer (ammonium lactate lotion 12%) was added to enhance the steroidal component of treatment and minimize potential localized skin reactions.
  - Findings showed that the combination of twice daily halobetasol with the moisturizer for 2 weeks had excellent clinical efficacy with an absence of adverse effects.
  - Subsequent reduction in the dosing frequency of halobetasol ointment to weekend-only use (known as weekend or pulse therapy) while continuing twice daily emollient therapy maintained initial clinical efficacy for a longer duration when assessed at 12 weeks.

- The use of a second agent, such as calcipotriol ointment, applied on weekdays in combination with a weekend-only regimen of halobetasol ointment has also been shown to increase the duration of remission versus weekend-only halobetasol alone when assessed at 6 months.[19]

Topical Treatment of Eczema

Atopic Eczema (AE)

AE is a chronic, pruritic, relapsing inflammatory skin disease.[20] The lifetime prevalence is estimated to be between 10-20% in children and 1-3% in adults.[21]

- The topical treatment approach includes reducing inflammation with topical corticosteroids or TCIs (i.e., tacrolimus or pimecrolimus).
- AE patients have a skin barrier abnormality,[22] as such, regular daily use of moisturizers to decrease transepidermal water loss is important. Recently, barrier repair creams[23] have become available for improving the skin barrier function. In an investigator-blinded, randomized trial of moderate to severe AE, a barrier cream reduced clinical disease and pruritus at 28 days of treatment comparably to fluticasone propionate 0.05% cream, a Class 5 corticosteroid.
- Avoidance of external irritants (e.g., harsh soaps, strong laundry detergents, and wool clothing) is beneficial.

Topical corticosteroids are the treatment of choice for AE; selection depends on disease severity and treatment site.

- For milder AE of the face and body folds, mild to moderate steroids (Class 6 or 7) are commonly used.
- For more severe AE and eczema on the trunk and extremities, more potent corticosteroids may be necessary (Class 4 or 5), but are best used only for a few weeks, then tapered to a milder preparation for maintenance. Generally, ointments work better than creams.
- Once the pruritus and thickness are controlled, switching to a TCI, such as tacrolimus ointment (0.03% for ages 2-15, 0.1% for >15 years), is very useful and helps to minimize side-effects from corticosteroids.
- If potent topical steroids are needed for long duration, consider pulse application at 1-2 times weekly dosing.

Chronic Hand Eczema (CHE)

CHE is a common condition and irritant dermatitis is more prevalent than allergic dermatitis. Early-onset hand eczema may be associated with atopy.

- A recent consensus statement on the management of CHE[24] suggested that topical therapy should include corticosteroids and TCIs.
- There is evidence of efficacy for long-term intermittent monotherapy with mometasone furoate cream.[25]
- For very refractory hand eczema, especially on the palms, superpotent topical corticosteroids can be helpful and side-effects, such as atrophy, are unusual when used on thick palmar skin.
- Möller[26] found the risk of recurrence of CHE was reduced by the very potent corticosteroid, clobetasol propionate, when used on an intermittent schedule of 2 applications a week, compared with a moderately potent corticosteroid cream.

Lichen Simplex Chronicus (LSC)

LSC is characterized by lichenification of the skin as a result of primary excessive scratching or rubbing.[27]

- When treated topically, often potent corticosteroid creams or ointments, such as betamethasone dipropionate, are necessary to control the pruritus and inflammation and to break the "itch-scratch" cycle.
- The use of potent topical corticosteroids under occlusion may be needed for successful treatment.
- Topical tacrolimus has been reported to be effective.[28]

Topical Treatment Suggestions for Recalcitrant Eczema

Atopic Eczema (excluding face and body folds)

- Potent topical corticosteroids for 2-3 weeks followed by tapering to a milder topical corticosteroid or TCI (i.e., Protopic™ ointment or Elidel® cream)
- Pulsed potent topical corticosteroid (i.e., fluocinonide 0.05% ointment/cream used twice daily Saturday and Sunday (use with caution in young children and if treating for longer than 2-3 weeks)
- Barrier repair creams (e.g., CeraVe®, EpiCeram®) can be tried in conjunction with topical corticosteroids or TCIs

Chronic Hand Eczema

- Superpotent topical corticosteroid for 2-3 weeks followed by tapering to a milder corticosteroid or TCI
- Superpotent topical corticosteroid with saran wrap or hydrocolloid occlusion overnight

Lichen Simplex Chronicus

- Superpotent topical corticosteroid for 2-3 weeks followed by tapering to a milder corticosteroid or TCI
- Superpotent topical corticosteroid with saran wrap or hydrocolloid occlusion overnight

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Relative Potency Class	Corticosteroid	%	Preparation
1	Betamethasone dipropionate glycol	0.05	Cream, ointment, lotion
	Clobetasol propionate	0.05	Cream, ointment, lotion, spray, shampoo
	Halobetasol propionate	0.05	Cream, ointment
2	Amcinonide	0.1	Cream, ointment, lotion
	Betamethasone dipropionate	0.05	Ointment
	Desoximetasone	0.05	Gel
	Desoximetasone	0.25	Cream, ointment
	Diflucortolone valerate	0.1	Cream, oily cream, ointment
	Fluocinonide	0.05	Cream, ointment, gel
	Halocinonide	0.1	Cream, ointment, lotion
3	Betamethasone dipropionate	0.05	Cream
	Betamethasone valerate	0.1	Ointment
	Mometasone furoate	0.1	Ointment
	Triamcinolone acetonide	0.5	Cream
4	Desoximetasone	0.05	Cream
	Fluocinolone acetonide	0.025	Ointment
	Hydrocortisone valerate	0.2	Ointment
	Mometasone furoate	0.1	Cream, lotion
	Triamcinolone acetonide	0.1	Ointment
5	Betamethasone valerate	0.1	Cream, lotion
	Fluticasone propionate	0.05	Cream
	Fluocinolone acetonide	0.025	Cream
	Hydrocortisone valerate	0.2	Cream
	Triamcinolone acetonide	0.1	Cream, lotion
6	Desonide	0.05	Cream, ointment, lotion
	Fluocinolone acetonide	0.01	Cream, lotion, oil
7	Hydrocortisone acetate	0.5-2.5	Cream, ointment, lotion

Table 1: Relative potency rankings of common topical corticosteroids in Canada

Disclaimer: I have tried to give evidence-based suggestions for treating these cutaneous diseases that can be chronic and recalcitrant to treatment. However, these are suggestions only and it must be remembered that potent topical corticosteroids can have significant side-effects as discussed. The guidelines of care for the use of topical glucocorticosteroids from the American Academy of Dermatology (reference 3) should be kept in mind, including the duration of use of superpotent and potent topical corticosteroids and maximal daily use. Extra caution needs to be given when using these agents in children. Close supervision by the prescribing physician is recommended.

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