Ceramide-based Moisturizers as Treatment for Pediatric Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory, xerotic and pruritic skin disease of increasing prevalence affecting 15-30% of children and 2-10% of adults.¹ AD and its associated health consequences present significant challenges to patients, particularly children and their families.² This includes unrelenting pruritus and an increased association with asthma, food allergies, allergic rhinitis and a predisposition to cutaneous infections.³ While the precise sequence of biochemical events leading to the development of AD is not fully understood, increasing evidence shows a complex interplay of environmental and genetic factors that affect the epidermal barrier and immune system. Barrier repair emulsions with good efficacy and safety profiles can mitigate the negative sequelae and help reduce the need for topical glucocorticosteroids.

Epidermal Barrier Dysfunction in the Pathogenesis of AD

The “Inside-Out” Effect

• The primary initiating mechanism in the pathogenesis of AD was thought to arise from an immune dysfunction leading to a T-helper cell 2 (Th2) polarized response, which results in disruption of the epidermal barrier.¹,³,⁴ This is known as the “inside-outside concept” of AD.

• The “inside-out” concept of AD pathogenesis has served as the cornerstone behind many of the current therapeutic strategies which target the dysfunctional immune system in AD.

• However, a growing body of evidence shows that a primary defect in the epidermal barrier, specifically the constituents of the cornified envelope, plays a major role in initiating and driving AD, in addition to the Th2 immune response.³

The “Outside-In” Effect

• The stratum corneum (SC) provides a water-tight barrier that prevents both internal fluid loss and penetration by hostile external organisms.

• Evidence suggests that rather than just forming a static physical wall the SC is able to sense and modulate its responses depending on different external physical, biological or chemical challenges.⁵,⁶,⁷ The penetration of the SC through any of these mechanisms results in the release of cytokines that can initiate, polarize and perpetuate the immune-inflammatory response of many inflammatory dermatoses. This is known as the “outside-in” concept.
The "outside-in" concept suggests that a primary defect present in the SC is a key driver of the inflammatory cascade of AD. This predisposes to increased trans-epidermal water loss (TEWL), inflammation, penetration of irritants, allergens, and secondary infection.8

Data now demonstrate the capacity of the cutaneous barrier to initiate and perpetuate AD including observations that:
1. Defects in the barrier result in elevated pH that activates proteases capable of directly inducing a TH2 inflammatory response.9
2. Severity of the barrier defect parallels AD severity.10,11
3. Barrier defect persists longer than both the clinical lesions and the underlying inflammation.11

**Morphological Changes in Epidermal Lipids in AD**

- The SC is made up of a multicellular, vertically stacked layer of cells embedded within a hydrophobic extracellular matrix.
- This matrix is derived from the secretion of lipid precursors and lipid hydrolases, both of which are secreted from lamellar bodies in the stratum granulosum.
- In physiological balance, the approximate proportions of the lipid component are predominantly composed of 50% ceramides, 25% cholesterol, and 10-20% free fatty acids.9
- In AD, there is a decrease in all three of these lipids, especially ceramides, which are found in both lesional and non-lesional skin.1
- A lipid imbalance and inadequate amounts of ceramides contribute to defective formation of the corneocyte lipid envelope and lipid mortar. This correlates with increased TEWL and enhanced barrier permeability.
- Moreover, ceramides may directly inhibit the immune response as evidenced by a very recent report showing that a ceramide-leukocyte mono-immunoglobulin-like receptor 3 (LMIR3) complex inhibited the activation of mast cells – a key mediator in pruritis.12
- In addition to ceramide defects, numerous exogenous factors can exacerbate barrier dysfunction, specifically soaps and surfactants in detergents that accelerate corneocyte and lipid degradation.
- Several antigens, including those from cockroaches, *Staphylococcus aureus*, dust mites, and scabies are also known irritants and can contribute further to the cycle of inflammation and pruritus.1

**Lipid Replacement Therapy in AD**

- Traditionally viewed as an immunological disorder, therapies for AD have included topical steroids and immunomodulators and sometimes more aggressive immunosuppressive agents that do not target the underlying structural barrier abnormalities.3,13
- Currently, emollients, ointments and oils thought to prevent epidermal water loss and inhibit sensitizing exogenous peptides from traversing the compromised barrier have become the first-line/adjunctive therapy in patients with AD.
- A new nonpharmacologic approach has emerged resulting from an improved understanding of AD etiopathogenesis. Aimed at barrier repair, ceramide-dominant, physiological lipid-based topical emulsions involve the delivery of balanced proportions of SC-specific lipids to assist in correcting epidermal barrier dysfunction.
- In addition to assisting in restoration of the lipid defect in AD, ceramide-based emulsions also help to normalize the pH of the skin, which is separately associated with a decrease in epidermal barrier integrity, increased inflammation, and reduced antimicrobial defenses.14,15

**Ceramide-based Emulsions in the Pediatric Population**

- Ceramide-based emulsions, such as EpiCeram® and TriCeram®, contain the physiological 3:1:1 molar ratio of ceramides, cholesterols, and free fatty acids, which emulates the endogenous composition of the SC and have been shown to repair SC integrity and function.16
- An analysis of the efficacy and safety of EpiCeram® used in 65 patients aged three months to 16 years with mild-to-moderate AD, showed that by week three of treatment 58% of participants had an Investigator Global Assessment rating of clear or almost clear. Further, pruritis severity decreased markedly by study week three, regardless of disease severity. Patient satisfaction was reported by 71% of the study population.17
- Data from a study done in 24 children with stubborn-to-recalcitrant AD who were receiving standard AD therapy demonstrated that the use of TriCeram® significantly improved Severity Scoring of Atopic Dermatitis (SCORAD) values in 22 of 24 patients by week three. Continued progressive improvement was seen in all patients between six and 21 weeks.18
- Although most early studies compared the efficacy of the three component mixtures (ceramides, cholesterols, free fatty acids) to vehicle alone, several recent reports have shown that some ceramide-dominant formulations can, on their own, induce improvements comparable to topical steroids in the treatment of mild to moderate disease.19,20
- CeraVe®, an over-the-counter (OTC) ceramide-dominant barrier repair cream, features multilamellar vesicular emulsions (MVEs), which are similar to liposomes but facilitate a 24-hour time-released delivery.
- Time-released MVEs offer once-daily application, thereby encouraging adherence to a simplified regimen of moisturizer use.
- While no standalone trials have been conducted with MVEs, the combination of MVEs with topical flucinonide 0.05% has recently been shown to reduce disease duration and time to clearance when compared with the same corticosteroid alone, resulting in accelerated skin barrier recovery.20
- This finding has recently been confirmed in a study which showed that twice daily use of CeraVe® cleanser and moisturizer over a 42-day period significantly improved skin condition and clinical outcomes on the SCORAD severity and quality of life aspects when comparing day 0 versus day 42 results.
- Moreover, the products were shown to be comfortable and were well tolerated when used in babies, children and adults with AD, with no significant adverse events reported.21
- Because ceramide-dominant formulations are not associated with dosing restrictions or adverse effects such as those seen
with corticosteroid treatment, they are suitable for patients of all ages and may be used on sensitive skin sites (e.g., face and intertriginous areas) which are prone to steroid-induced atrophy.

**Other Non-steroidal Barrier Repair Products**

- While ceramide-based moisturizers appear to be superior to most non-ceramide OTC moisturizers, a recent trial showed the use of a glycyrrhetinic acid-containing barrier repair cream (Atopiclair®) resulted in improvement of mild to moderate AD in children that was equivalent to EpiCeram®.22
- A recent study of topical pimecrolimus demonstrated non-superiority when compared with a number of different OTC creams (collectively regarded as one group), further suggesting that correction of numerous epidermal barrier derangements may be an effective way of controlling AD.14

**Conclusion**

Because AD follows a chronic, relapsing course it is essential that, in addition to pharmacologic intervention, hydration and proper barrier function of the SC is maintained with daily regimented moisturizer use as part of ongoing therapy. Adequate moisturization reduces the need for drug treatments and limits the severity and frequency of eczematous flares. Clinical data demonstrate that correction of the skin barrier defects through emollient therapy inhibits downstream drivers of the inflammatory response, thereby providing the rationale for prophylactic and continuous use. Ceramide-based moisturizers have demonstrated efficacy in reducing TEWL, improving barrier function, and maintaining hydration of the SC. Further, they have an excellent safety profile, and can be safely used in patients of all ages.

**References**

Androgenetic Alopecia: A Review of Topical Agents for Hair Growth Promotion

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Introduction

Hair loss is a common dermatological problem that affects a large segment of the population both physically and psychologically. While there are many causes of hair loss, such as telogen effluvium and alopecia areata, androgenetic alopecia (AGA) also called male pattern hair loss (MPHL), is the most common. Hair loss can start anytime at or after puberty. Its occurrence and severity increases with age, with at least 80% of Caucasian men displaying signs of MPHL by age 70. Because of its considerable psychological impact, many patients seek treatment. Currently, only one topical agent is approved for treatment of hair loss in men, although other treatments are being clinically investigated.

Pathogenesis

- The pathophysiology of AGA remains to be fully determined however, as the name implies, androgens and a genetic predisposition appear to be involved.
- Inherited AGA is polygenic with input from either or both parents.
- The androgenic hormones testosterone (T) and dihydrotestosterone (DHT) are the most important in regulating the anagen duration and hair matrix volume.
- DHT, a potent metabolite of testosterone, enlarges follicles in the beard, chest and limbs and miniaturizes follicles in the bitemporal region. In genetically susceptible patients, DHT can cause miniaturisation in the vertex and frontal hairline leading to AGA-patterned thinning.
- The conversion of T to DHT occurs at the hair follicles, elicited by a type II 5 alpha-reductase enzyme.

Clinical Presentation & Diagnosis

- AGA presents with fronto-temporal recession and over the vertex: the occipital scalp is preserved.
- Diagnosis is made based on the clinical history; however a scalp biopsy may be needed in situations where the cause of hair loss is uncertain.

Current Topical Treatments

Minoxidil

- Minoxidil is the current topical standard treatment of hair loss. Initially used as an oral antihypertensive medication, its association with hypertrichosis led to its development as a topical therapy for AGA.
- Minoxidil 2% solution was approved by the US FDA for the treatment of MPHL in 1988, and was subsequently approved in 5% strength in a solution format in 1997 and in a foam format in 2006. The 2% solution formulation alone was approved in the US for female pattern hair loss in 1996. Minoxidil 2% solution became available in Canada for the treatment of MPHL in 1986, and the 5% foam in November 2012.
- The content discussed here relates to the branded formulation of minoxidil only and not the compounded or generic formulations.
- The precise mechanism of action of minoxidil is unknown; however it is associated with vasodilation, angiogenesis and enhanced cell proliferation, probably mediated via potassium channel opening. Further, it has been seen to prolong duration of anagen of the hair cycle, increase miniaturized hair follicle size, and preserve and thicken preexisting hair.
- Data from a 16-week, randomized, double-blind, placebo controlled (RCT) study of the newly approved minoxidil 5% foam application show at weeks 8, 12 and 16 the mean increase in target area hair count was significantly greater than placebo (p<0.0001). At week 16 the percentage change in target area hair count was 13.4% in men treated with minoxidil 5% foam compared with 3% for the placebo arm (21.0 hairs/cm² vs. 4.3 hairs/cm², respectively). Further, 38.3% of patients in the minoxidil arm demonstrated increased hair growth at week 16, compared with 5.2% in the placebo group (p<0.0001), as rated by an expert panel.
• Data from a 48-week RCT also showed an increase in target area hair count in men treated with minoxidil solution, and that the product reversed hair loss as well as slowed its progression.8

• The same study also showed that target area hair counts were greater with the 5% solution compared with the 2% minoxidil solution.

• Minoxidil treatment is life-long: stopping treatment will result in a shedding of all minoxidil-dependent hair growth within 4-6 months after cessation of therapy.9

• The recommended dosing of minoxidil 2% solution is twice daily topical application of 1 ml spread evenly over the top of the dry scalp in the hair loss area.

• With minoxidil 5% foam, half a capful is applied twice daily on the dry scalp and left in place for at least four hours. To avoid the drug coming into contact with the face and limit the risk of hypertrichosis in non-scalp body areas, patients should wash their hands with warm water after application.

• Minoxidil has a well-established safety profile. The most frequently reported adverse drug reaction following the short-term, 16-week treatment with minoxidil 5% foam was headache.7 The most frequently reported dermatological adverse events were erythema, rash, acne, and pruritus. In long-term treatment, the most frequently reported non-serious adverse events were infection and accidental injury.7

• The most frequently reported adverse events in the minoxidil 2% solution clinical trials were minor respiratory events, including colds and respiratory infections, rhinitis, sinusitis and coughing. Dermatologic adverse reactions were the next most frequent and included scaling, itching and rash.7

• Increased hair shedding is possible in the first 2-6 weeks of treatment, which likely results from inducing anagen from the resting phase.7 This may be an indication that minoxidil is effective; patients should be advised not to stop treatment if they experience hair loss for two weeks or less. However, if hair loss continues for longer than two weeks, patients should be advised to stop using the product and talk to their doctor.7

• Careful evaluation of the risks and benefits of minoxidil treatment should be considered in patients with pre-existing cardiac, renal or hepatic disease or scalp abnormalities and those receiving potentially interacting drugs concomitantly (e.g., hypotensive agents, such as guanethidine). If minoxidil therapy is initiated in these scenarios, patients should be closely monitored.9

• Allergic reaction to minoxidil is rare. Constituents of the vehicles may cause skin irritation. Irritant dermatitis to propylene glycol (a component of minoxidil 2% solution vehicle) may occur. Patch testing for propylene glycol can be performed as a precaution. If contact dermatitis results from minoxidil use, treatment should be stopped.

• Minoxidil 5% foam is propylene glycol free. Further, it is aesthetically more pleasing to patients compared to the solution, and thus likely increases compliance.

• Data show patients using the foam product rated it significantly higher compared with the minoxidil solution, finding it easy to apply, quick to absorb and non-drip.9

• Systemic absorption of minoxidil is weak with only 0.3 - 4.5% reaching the circulation. It is excreted within four days.

### Other Topical Agents

#### Prostaglandins

• The prostaglandin F2α analogues latanoprost and bimatoprost are widely used to treat glaucoma.

• Bimatoprost topical solution 0.03% is approved for treating hypotrichosis of the eyelashes by increasing their growth including length, thickness and darkness.

• Topical latanoprost is under investigation for the treatment of AGA.10

#### Ketoconazole

• Ketoconazole is an imidazole antifungal agent known to be effective for treatment of seborrheic dermatitis and dandruff. It is available as an over-the-counter topical shampoo at a 2% strength.

• Ketoconazole’s action on scalp microflora may benefit patients with AGA-associated follicular inflammation.11,12

• While the mechanism by which ketoconazole may improve hair growth is unclear, it is known to have anti-inflammatory effects against T-cells which are found in the balding area in patients with AGA.13 Further, it decreases colonization of the skin by Malassezia. It also inhibits steroid synthesis and decreases DHT levels at the hair follicle by affecting androgen receptor activity.13

### Conclusion

AGA is a common issue among men and can significantly affect self-esteem and quality of life, such that they may seek treatment. While different topical agents are currently being investigated for safety and efficacy, only one topical treatment, minoxidil, is currently approved for hair regrowth. The newly approved 5% foam solution has demonstrated patient preference, which in turn may improve compliance. Given its established efficacy and safety profile, minoxidil may be useful in the topical management of AGA in male patients.

### References

7. ROGAINE® Canadian Product Monograph
Adjunctive Skin Care for Acne

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Introduction

Acne vulgaris (AV) is among the most common dermatological disorders seen by dermatologists, affecting approximately 85% of people between the ages of 12 and 24 years. Emerging evidence suggests that acne is associated with epidermal barrier impairments, including stratum corneum (SC) barrier permeability. There is also mounting evidence to demonstrate an association between AV and inherent epidermal barrier dysfunction involving increased filagrin expression and decreased ceramide levels. While topical therapy remains a key therapeutic approach in the clinical management of AV, it can be associated with side effects that may compromise the SC and impair patient adherence. The use of adjunctive cleansers and moisturizers can help mitigate treatment side effects and subsequently enhance therapeutic efficacy.

Pathophysiology & Clinical Presentation

• The four main pathophysiologic features of AV are:
  1. Androgen-mediated stimulation of sebaceous gland activity
  2. Abnormal keratinization leading to follicular plugging (comedone formation)
  3. Proliferation of Propionibacterium acnes (P. acnes) within the follicle
  4. Inflammation

• Genetic factors, stress and diet may also influence the development of acne.

• Some data suggest that patients with AV suffer from inherently compromised facial SC barrier permeability, and that the severity of AV may correlate with the degree of SC barrier impairment and decreased levels of free sphingosine and total ceramides, suggesting a deficiency of the intercellular lipid membrane.

• Some medications used to treat AV can alter SC integrity and function, either via the active ingredient, the vehicle, or both. This can result in signs and symptoms of cutaneous irritation such as erythema, scaling and a burning or stinging sensation.

• Recent data show that the experience of just one treatment-related side effect (e.g., irritation, dryness, redness) significantly, negatively impacts adherence to acne treatment.

Topical Therapy

Topical therapy is used for mild to moderate acne and also for maintenance therapy in all severity levels (Table 1).

• Evidence-based treatment guidelines recommend fixed-dose combination topical benzoyl peroxide (BPO)-adapalene or BPO-clindamycin for treatment of mild-moderate papulopustular acne.

• Retinoids are comedolytic, anticomedogenic and anti-inflammatory.

• BPO is an antimicrobial agent that has some keratolytic effects and does not contribute to antibiotic resistance.

• Antibiotics have antimicrobial and anti-inflammatory effects. They can be used in conjunction with BPO lotion, gel or wash to limit antibiotic resistance. They should not be used for maintenance therapy.

• Topical dapsone gel is antimicrobial and antineutrophilic.

• New fixed-dose retinoid-based combination therapies are available (e.g., tretinoin and clindamycin)

• Both topical retinoids and BPO can cause symptoms of skin irritation.

<table>
<thead>
<tr>
<th>Acne Pathogenic Factors</th>
<th>Retinoids</th>
<th>Benzoyl Peroxide</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adapalene</td>
<td>Tazarotene</td>
<td></td>
</tr>
<tr>
<td>Normalizes keratinization and desquamation</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 1: Topical acne therapies and their pathogenic targets
Cleansers & Moisturizers

- The goal of cleansing for patients with acne or acne-prone skin is to remove surface dirt, sweat, excess oil, exfoliated cells and micro-organisms without irritating or disrupting the skin's protective barrier.
- Regular use of mild cleansers is an important component of effective acne management as a hydrated SC absorbs medication more readily and is less prone to irritation.
- Routine cleansing may enhance antimicrobial activity and decrease the risk of infection.
- Simplified treatment and skin care regimes should be recommended, including the use of an appropriate moisturizer and washing with a mild, soap-free cleanser twice daily.²

Types of Cleansers

- To date, limited published data exist to inform the clinical management of AV with regard to cleansers and moisturizers. Recommendations are based largely on general knowledge (e.g., non-soap based cleansers).
- Ideally, cleansers for acne skin should be: non-comedogenic, non-acnegenic, non-irritating, and non-allergenic.⁶
- A wide spectrum of skin cleansing agents exist for acne ranging from lipid free cleansers, syndets and astringents to exfoliants and abrasives.⁷
- Anionic detergents (i.e., soaps) can alter the natural pH of skin, which is normally between 5.3 and 5.9.
- An increase in pH can result in increased transepidermal water loss (TEWL), which causes dryness. Further, an increase in pH may facilitate microbial growth, which can exacerbate AV.⁸
- Abrasive cleansers can promote SC barrier dysfunction and contribute to signs and symptoms of irritation: these should be avoided.
- Suitable cleansers for acne-prone skin are generally based on mild synthetic surfactants that minimize the potential for skin barrier disturbances.
- Non-ionic surface-acting agents (e.g., silicone and polysorbate) are less likely to cause irritation and are formulated to the same pH as the skin (5.5).
- Silicone surfactants (e.g., dimethicone) such as Spectro®, are effective at eliminating surface debris without completely stripping away protective oils.
- Cleansers that contain zinc coceth and zinc gluconate, such as Cetaphil® DermaControl, also provide astringent properties without irritation or alteration to the pH level of the skin, and the zinc complex absorbs excess oil for a matte appearance of the skin.
- Cleansers containing emollients, such as Cetaphil® DermaControl, Effasclar, Spectro® and Cetaphil® Gentle Skin Cleanser can minimize damage to the SC barrier by emulsifying dirt and oil for easy removal. Additionally, Cetaphil® DermaControl contains humectants, which attract moisture to the skin in order to alleviate the drying effects of cleansing.

Types of Moisturizers

- Effective moisturizers combine humectants and emollients to prevent or reduce water evaporation, draw moisture up from deeper layers, alleviate xerosis and maintain skin barrier integrity.
- Moisturizers should also prevent primary irritation.
- Broad spectrum UVA/UVB sun protection is also important for patients with AV, particularly for those on topical and systemic retinoid therapy.⁹
- The different types of moisturizers include (Table 2): 1. Occlusives 2. Humectants 3. Emollients 4. Protein rejuvenators¹⁰ 5. Ceramide dominant
- Moisturizers containing ceramides have recently entered the market and work to replace naturally occurring lipids in the SC.
- The only published clinical trial data studying an adjunctive moisturizer in AV patients concerns Cetaphil® DermaControl. It contains ceramides and an oil-absorbing zinc complex. It is non-comedogenic, non-irritating, non-acnegenic and non-greasy.
- The recent development of oleosome technology, which is also present in Cetaphil® DermaControl, enables the delivery of broad spectrum UVA/UVB sun protection (SPF 30). This technology effectively reduces the concentration of filters being applied to the skin, decreasing the potential for skin sensitivity reactions.⁹

Acne Therapy & Adherence

- Treatment adherence in patients with AV is a significant problem and is documented at approximately 50%.³
- An estimated 30-40% of patients using topical acne treatment formulations do not comply with their prescribed regimen.¹¹
- Clinical variables that have been shown to negatively impact adherence include age, patient satisfaction with treatment, and knowledge about acne treatment.⁴
- Irritation resulting from topical medications and the emergence of bacterial resistance to both topical and oral antibiotics remain significant barriers to good treatment adherence.
- Recent advances in vehicle technology have improved efficacy, local tolerance and adherence.¹²
- Additionally, novel delivery mechanisms and vehicles, such as pumps and foams, are convenient and preferred by patients, which may also improve adherence.¹³
- The appropriate selection and use of moisturizers has positive effects on treatment adherence.⁴
- Patient satisfaction with treatment and clinical improvement as evaluated by a dermatologist have been shown to improve treatment adherence and may also improve patient self-esteem.⁴
- Discuss realistic treatment expectations with patients and consider dosing strategies that can enhance adherence (Table 3).
Adjunctive Skin Care in Acne: Clinical Evidence

- Alleviating dryness and improving skin comfort by using a moisturizer concurrently with retinoid therapy could enhance treatment efficacy. Data from a randomized, split-face study showed the application of a moisturizing cream applied twice daily for 15 days by patients taking either oral isotretinoin (10-20 mg) for two months or topical tretinoin 0.05% for one month provided significant improvements, compared with baseline, in the levels of skin dryness, roughness and desquamation induced by either drug. As well, skin properties and discomfort were substantially improved.

- Results from a study evaluating a facial moisturizer with SPF 30 and ceramide precursor formulated for blemish prone skin with 0.05% tretinoin found a patient preference for the moisturizer. It was a randomized, investigator-blinded, split-face study assessing erythema, scaling and dryness in patients with blemish prone skin. While both sides developed skin irritation, it worsened in the non-moisturized sides. Notably, all five parameters, namely erythema, scaling, dryness, stinging/burning and pruritus were improved on the sides treated with moisturizer.

- Adjunctive use of moisturizer with a topical tretinoin cream improved tolerance of the treatment.

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<table>
<thead>
<tr>
<th>Type</th>
<th>Mode of Action</th>
<th>Example ingredient</th>
<th>Indication</th>
<th>Possible side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Occlusive</td>
<td>It physically blocks water loss</td>
<td>- Petrolatum</td>
<td>- Xerosis</td>
<td>- Messy</td>
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<tr>
<td></td>
<td></td>
<td>- Lanolin</td>
<td>- Atopic dermatitis</td>
<td>- Some can cause folliculitis (mineral oil)</td>
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<tr>
<td></td>
<td></td>
<td>- Mineral oil</td>
<td>- Prevention of irritant contact dermatitis</td>
<td>- May cause pimples</td>
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<tr>
<td></td>
<td></td>
<td>- Silicones</td>
<td></td>
<td>- Some may cause contact dermatitis (lanolin)</td>
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<td></td>
<td></td>
<td>- Zinc oxide</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Caprylic triglyceride</td>
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<td></td>
<td></td>
<td>- Lecithin</td>
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<tr>
<td>2. Humectants</td>
<td>Attracts water to the SC</td>
<td>- Glycerin</td>
<td>- Xerosis</td>
<td>- Some may cause irritation (urea, lactic acid)</td>
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<td></td>
<td></td>
<td>- Sorbitol</td>
<td>- Ichthyosis</td>
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<td></td>
<td></td>
<td>- Urea</td>
<td>- Skin rejuvenation</td>
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<td>- Alpha-hydroxy acids</td>
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<td></td>
<td></td>
<td>- Sorbitol</td>
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<td></td>
<td>- Panthenol</td>
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<td></td>
<td></td>
<td>- Pentylene glycol</td>
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<td></td>
<td></td>
<td>- Sodium hyaluronate</td>
<td></td>
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<td></td>
<td></td>
<td>- Arginine</td>
<td></td>
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<td></td>
<td></td>
<td>- Sodium pyrrolidone carboxylic acid (PCA)</td>
<td></td>
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<tr>
<td>3. Emollients</td>
<td>Smooths skin by filling the spaces</td>
<td>- Diisopropyl sebacate</td>
<td>- Reduces skin roughness</td>
<td>- Not always effective</td>
</tr>
<tr>
<td></td>
<td>between skin flakes with droplets of oil</td>
<td>- Isopropyl lauroyl sarcosinate</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Sunflower seed oil</td>
<td></td>
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<td></td>
<td></td>
<td>- Shea butter</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Caprylyl glycol</td>
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<td></td>
<td></td>
<td>- Dimethicone</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- Cetyl alcohol</td>
<td></td>
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<tr>
<td>4. Rejuvenators</td>
<td>Claim to rejuvenate the skin by</td>
<td>- Collagen</td>
<td>- Skin rejuvenation</td>
<td>- Unlikely to work as protein molecules are too large to cross the epidermis</td>
</tr>
<tr>
<td></td>
<td>replenishing essential proteins</td>
<td>- Keratin</td>
<td></td>
<td>- Some may cause contact dermatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Elastin</td>
<td></td>
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<tr>
<td>5. Ceramide</td>
<td>Replaces ceramides deficient in skin</td>
<td>- ceramides, pseudoceramides, ceramide precursors</td>
<td>- Ceramide lipid replacement</td>
<td>- Efficacy may be impaired in severe disease</td>
</tr>
<tr>
<td>dominant</td>
<td>barrier</td>
<td></td>
<td>- SC lipid barrier repair</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Prevention of TEWL</td>
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<td></td>
<td></td>
<td></td>
<td>- Occlusive effect to prevent water loss,</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>repair lipid layers, restore barrier</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Types of moisturizers
Conclusion
Skin barrier impairment in patients with A V can negatively impact acne treatment. Therefore, providing patient-specific skin care recommendations, including product selection and proper use, is an important part of the clinical management of A V and may improve patient tolerance to treatment. The adjunctive use of appropriate gentle soap-free cleansers and non-comedogenic moisturizers, ideally products that also restore SC barrier function, provide SPF protection and reduce side effects of topical acne therapy, are recommended. Moreover, they are preferred by patients and will likely improve treatment adherence.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical therapy active</td>
<td>• careful selection of topical therapy</td>
</tr>
<tr>
<td></td>
<td>• partially solubilized or micronized retinoid</td>
</tr>
<tr>
<td></td>
<td>• combination therapy to minimize irritation</td>
</tr>
<tr>
<td>Topical therapy vehicle</td>
<td>• cream&gt;gel</td>
</tr>
<tr>
<td></td>
<td>• hydrogel&gt;alcohol gel</td>
</tr>
<tr>
<td></td>
<td>• excipients (humectants, emollients)</td>
</tr>
<tr>
<td>Application technique</td>
<td>• applied to dry face every night with emollient</td>
</tr>
<tr>
<td></td>
<td>• consider alternate days</td>
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<tr>
<td></td>
<td>• consider short contact</td>
</tr>
<tr>
<td>Adjunctive skin care</td>
<td>• gentle, non-comedogenic cleanser and emollient</td>
</tr>
<tr>
<td>Counselling</td>
<td>• expectations</td>
</tr>
<tr>
<td></td>
<td>• application technique</td>
</tr>
<tr>
<td></td>
<td>• strategies to mitigate adverse events</td>
</tr>
</tbody>
</table>

Table 3: Strategies to reduce irritation associated with topical acne therapy

References
## Skin Treatments Introduced in 2012

<table>
<thead>
<tr>
<th>Type/Class of Therapy</th>
<th>Generic/Trade/Company Names</th>
<th>Indication</th>
<th>Approving Regulatory Agency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acne</strong></td>
<td>Adapalene 0.1% + benzoyl peroxide 2.5% gel <em>Epiduo</em>® Galderma Laboratories</td>
<td>This gel formulation of adapalene and benzoyl peroxide was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
<td>US FDA</td>
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<tr>
<td></td>
<td>Adapalene 0.3% gel <em>Differin</em>® Galderma Laboratories</td>
<td>A pump dispenser for this retinoid gel formulation was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td>Tazarotene 0.1% foam <em>Fabio</em>™ Stiefel Laboratories</td>
<td>A new retinoid formulation was approved for the topical treatment of acne vulgaris in patients ≥12 years of age.</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td>CIP-Isotretinoin capsule <em>Epuris</em>™ (in Canada) <em>Absorica</em>™ (in US) Cipher Pharmaceuticals</td>
<td>Approval was granted to this novel formulation of isotretinoin for the treatment of severe recalcitrant nodular acne. It offers a precise, consistent, and uniform dosage delivery with an absorption characteristic that is stable with or without food when compared with traditional generic isotretinoin.</td>
<td>Health Canada</td>
</tr>
<tr>
<td><strong>Actinic Keratosis</strong></td>
<td>Ingenol mebutate gel (0.015%, 0.05%) <em>Picato</em>® Leo Pharma Inc.</td>
<td>Ingenol mebutate gel (derived from the <em>Euphorbia peplus</em> plant) received approval for the topical treatment of actinic keratosis. The 0.015% formulation is used once-daily on the face and scalp for 3 consecutive days, and the 0.05% gel is used once-daily on the trunk and extremities for 2 consecutive days. The treatment course may be completed in 2-3 days.</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td>Imiquimod 3.75% cream <em>Zyclara</em>® Meda AB</td>
<td>Marketing authorization was granted to this immune response modifier for the topical treatment of actinic keratosis. Regulatory approval is valid in all European Union countries.</td>
<td>European Commission</td>
</tr>
<tr>
<td><strong>Anesthetic</strong></td>
<td>Lidocaine 7% + tetracaine 7% cream <em>Pliaglis</em>® Nuvo Research Inc. Galderma Laboratories</td>
<td>Approval was granted to this topical local anesthetic cream indicated for use on intact skin in adults to provide local analgesia for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.</td>
<td>Health Canada</td>
</tr>
<tr>
<td></td>
<td>Poly-ureaurethane 16% nail solution <em>Nuvail™</em> Innocutis Medical</td>
<td>This poly-ureaurethane 16% nail solution was approved for the management of fragile, damaged or brittle nails with cracking or splitting (referred to as nail dystrophy). It mechanically supports the damaged nail plate, forming a barrier that protects from further injury and strengthens the nail.</td>
<td>US FDA</td>
</tr>
<tr>
<td><strong>Brittle Nail Syndrome</strong></td>
<td>Hylauronic acid-based dermal filler <em>Belotero® Balance</em> Merz Aesthetics/Anteis SA</td>
<td>This hyaluronic acid-based cohesive gel dermal filler was approved for the temporary correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.</td>
<td>US FDA</td>
</tr>
<tr>
<td></td>
<td>Hylauronic acid injectable gel <em>Restylane-L</em>® Medicis Aesthetics</td>
<td>Approval of an additional indication was granted to this transparent hyaluronic acid gel dermal filler to include submucosal implantation for lip augmentation in patients &gt;21 years of age.</td>
<td>US FDA</td>
</tr>
<tr>
<td><strong>Dermal Fillers and Injectables</strong></td>
<td>Collagenase clostridium histolyticum <em>Xiaflex</em>® Actelion Pharmaceuticals Auxilium Pharmaceuticals</td>
<td>Approval was granted to this novel, first-in-class biologic for the treatment of Dupuytren's contracture in adults with a palpable cord. The injected enzymes dissolve and weaken the contracted collagen cord. It is the only nonsurgical option for Dupuytren's disease.</td>
<td>Health Canada</td>
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<tr>
<td><strong>Dupuytren's Contracture</strong></td>
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<tr>
<td>Disease</td>
<td>Product Description</td>
<td>Approval Authority</td>
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<td>-----------------------------------------</td>
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<tr>
<td>Hereditary Angioedema</td>
<td>C1 esterase inhibitor (human) <em>Cinryze®</em> ViroPharma Incorporated</td>
<td>Health Canada</td>
<td></td>
</tr>
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<td></td>
<td>This highly purified, pasteurized and nanofiltered plasma-derived C1 esterase inhibitor product was approved for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema.</td>
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<tr>
<td>Herpes Zoster Virus (VZV) Infection</td>
<td>Varicella zoster immune globulin (human) injection <em>Varizig®</em> Cangene Corporation</td>
<td>US FDA</td>
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<td></td>
<td>This varicella zoster immune globulin preparation was approved for reducing the severity of chicken pox infections in high risk individuals when given within 4 days after exposure. It is the only FDA approved immune globulin for VZV post-exposure prophylaxis treatment available in the US.</td>
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<tr>
<td>Lice</td>
<td>Ivermectin 0.5% lotion <em>Sklice™</em> Sanofi Pasteur U.S.</td>
<td>US FDA</td>
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<td>Approval was granted to this broad-spectrum antiparasitic agent for the topical treatment of head lice in patients ≥6 months of age. Most infestations are eradicated with a single 10-minute application and without nit combing.</td>
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<td>Melanoma</td>
<td>Ipilimumab <em>Yervoy™</em> Bristol-Myers Squibb</td>
<td>Health Canada</td>
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<td>This human monoclonal antibody was approved for the treatment of metastatic melanoma. Administered intravenously, the drug blocks a T-lymphocyte antigen (CTLA-4), altering the body's ability to fight off cancerous cells and allowing the immune system to recognize, target, and attack cells in melanoma tumors.</td>
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<td><strong>Vismodegib capsule <em>Erivedge™</em> Genentech Roche Group Curis, Inc.</strong></td>
<td>US FDA</td>
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<td>Approval was granted to this hedgehog pathway inhibitor for the treatment of adults with advanced basal cell carcinoma (BCC). The drug is administered orally once-daily and is indicated for patients with locally advanced BCC who are not candidates for surgery or radiation and for patients with metastatic BCC.</td>
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<td><strong>Vemurafenib tablets <em>Zelboraf™</em> Genentech/Roche Group Plexxikon/Daiichi Sankyo Group</strong></td>
<td>European Commission</td>
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<tr>
<td></td>
<td>Approval was granted to this oral, small molecule, kinase inhibitor for the treatment of metastatic or unresectable melanoma. Therapy is specifically indicated for patients with BRAFV600E mutation-positive melanoma. This BRAF enzyme inhibitor was approved with a companion diagnostic called the cobas® 4800 BRAF V600 Mutation Test, which determines a patient's eligibility for treatment.</td>
<td>Health Canada</td>
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<tr>
<td>Psoriasis</td>
<td>Calcipotriene 0.005% + betamethasone dipropionate 0.064% topical suspension <em>Taclonex®</em> LEO Pharma Inc.</td>
<td>US FDA</td>
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<td>This topical suspension of a vitamin D analog with a corticosteroid was approved for the treatment of body plaque psoriasis. This formulation is a first-line single therapy that is indicated for once-daily treatment of both scalp and body plaque psoriasis for up to 8 weeks.</td>
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<tr>
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<td><strong>Calcipotriene 0.005% foam <em>Sorilux™</em> Stiefel, a GSK Company</strong></td>
<td>US FDA</td>
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<td></td>
<td>A supplemental New Drug Application (sNDA) was approved for calcipotriene foam 0.005%, expanding the sanctioned indications to include the topical treatment of plaque psoriasis of the scalp. With these recent changes, this topical synthetic vitamin D3 analog is now indicated for the treatment of plaque psoriasis of the scalp and body in patients &gt;18 years of age.</td>
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<td>Psoriatic Arthritis</td>
<td>Delayed-release prednisone tablets <em>Rayos®</em> Horizon Pharma, Inc.</td>
<td>US FDA</td>
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<td>A delayed-release corticosteroid was approved as an anti-inflammatory or immunosuppressive agent to treat a wide spectrum of diseases including rheumatoid arthritis, psoriatic arthritis, polymyalgia rheumatica, ankylosing spondylitis, asthma, and chronic obstructive pulmonary disease (COPD).</td>
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