Topical Acne Therapy: Current and Advanced Options for Optimizing Adherence

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Introduction

Acne is the most common skin disorder treated by physicians, affecting about 85% of individuals between the ages of 12-24 years. Adult-onset acne is increasingly common with presentation in patients beyond their teenage years. Topical treatment is the mainstay for mild disease and adjunctive to oral or hormonal therapy for moderate acne. However, patients often consider topical medications to be time-consuming and inconvenient to use, irritating to the skin, and less potent than systemic therapy. These factors can engender nonadherent behaviour and treatment dissatisfaction. This article explores recent formulary advances and offers clinical strategies that can encourage adherence and improve treatment outcomes.

Prevalence

Adolescent Acne

- The primary cause is attributable to increased hormonal activity that triggers sebum production.
- Onset ranges between ages 10-13 years, generally resolving by the early 20s.
- Areas of frequent involvement include the cheeks, chin, forehead, and nose. In severe cases, the back, chest, neck, shoulder, and upper arms can be affected.
- Severe disease is more prevalent among males.
- Teenagers and adult females are particularly susceptible to the negative psychosocial impacts of acne, which can result in low self-esteem and self-confidence, an inferior body image, and avoidance of social interactions.

Post-adolescent Acne

- Evidence suggests that adult/mature acne is increasing in prevalence, and with this trend, a growing concern regarding the potential for serious psychosocial concomitants (e.g., depression and anxiety) in affected individuals.
- There are two generally accepted types:
  1. Persistent acne refers to acne that does not clear by the mid-20s. Lesions commonly develop on the lower face.
  2. Late-onset acne may be caused by hormones, stress, bacterial colonization, and cosmetics. As with persistent acne, the lower face is most frequently affected, but lesions can also occur on the back and chest.
- This variant is more prevalent in women; it frequently affects perioral regions (i.e., the chin, around the mouth, and along the jaw line) and flares premenses.
Combination Therapy with BPO

Advances in topical acne agents have:

- led to retinoid derivatives that are photostable and more chemically stable, even in the presence of an oxidizing agent, such as BPO.
- permitted the use of tretinoin gel microsphere (TGM) and adapalene in the morning, or directly before or after BPO application.
- decreased the emergence of bacterial resistance due to the addition of BPO to topical antibiotic agents, and the use of BPO with long-term oral antibiotics.

Vehicle Technology in Topical Acne Preparations

- Many new topical acne formulations have aqueous-based gel vehicle delivery systems that do not contain alcohol and are suitable for use in all skin types.
- A once-daily formulation of clindamycin in a foam vehicle improves absorption and cosmetic acceptability, and facilitates ease of use, especially over larger or hair-bearing areas.
- Clindamycin 1% + BPO 5% gel formulation includes both glycerin (humectant) and dimethicone (emollient) to reduce both epidermal barrier impairment and cutaneous irritation, and increase hydration.

Microsphere Technology and Pump Delivery System

Tretinoin has been formulated with a patented microsphere delivery system in a novel metered pump bottle, which allows for accurate dosing and clean dispensing when compared with tubes. These advances have resulted in:

- less irritation due to the slow release of tretinoin from the microspheres into the epidermis.
- improved photostability, allowing for morning use.
- improved ease of use. TGM is a water-based gel that can be applied to the face immediately after washing.
- an innovative dispensing system (i.e., a dual chambered pump dispenser that releases the correct and consistent pea-sized amount for full face application).
- Controlled dispensing of tretinoin limits irritation, which can encourage medication adherence.
- The pump system allows simple dosing instructions (e.g., apply 2 pumps to the affected facial area).
- A multicenter trial of 544 acne patients who were dissatisfied with their current treatment used TGM for 12 weeks. Most patients (82.3%) rated the pump as an excellent or very good method of dispensing acne medication. The tretinoin pump system significantly increased adherence, quality of life, and treatment satisfaction for study patients.

Table 1. The spectrum of approved topical acne medications

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Topical Acne Agents</th>
<th>Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Benzoyl peroxide (BPO)</td>
<td>Directed against <em>Propionibacterium acnes</em></td>
</tr>
<tr>
<td></td>
<td>Clindamycin</td>
<td>Formulated in creams, ointments, lotions, gels, and foams</td>
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<tr>
<td></td>
<td>Erythromycin</td>
<td>One product is also available with SPF 15 + antibiotic</td>
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<tr>
<td></td>
<td>Sodium sulfacetamide</td>
<td>BPO may induce irritation and dryness; it fades coloured fabrics</td>
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<tr>
<td></td>
<td></td>
<td>BPO is the most common OTC antiacne agent</td>
</tr>
<tr>
<td>Combination</td>
<td>BPO + antibiotic</td>
<td>Facilitates treatment of multiple pathogenic factors</td>
</tr>
<tr>
<td>products</td>
<td>Retinoid + antibiotic</td>
<td>Gel formulations</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Adapalene</td>
<td>Combined efficacy is greater than either agent alone</td>
</tr>
<tr>
<td></td>
<td>• photostable</td>
<td>Simplifies treatment regimen and reduces dosing frequency</td>
</tr>
<tr>
<td></td>
<td>• can be applied in the morning</td>
<td>Combined use of BPO + topical antibiotic can reduce bacterial resistance; once opened, these products have a limited shelf-life (3-4 months)</td>
</tr>
<tr>
<td></td>
<td>Tazarotene</td>
<td>May be used for all grades of acne and for maintenance therapy</td>
</tr>
<tr>
<td></td>
<td>• photostable</td>
<td>Retinoids may enhance the penetration of other topical agents (i.e., antibiotic + BPO)</td>
</tr>
<tr>
<td></td>
<td>• can be applied in the morning</td>
<td>Microsphere technology stabilizes tretinoin and inhibits photodegradation</td>
</tr>
<tr>
<td></td>
<td>Tretinoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• photolabile (not microsphere)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• best applied in the evening</td>
<td></td>
</tr>
</tbody>
</table>
Novel combinations and new uses of existing agents are expanding the spectrum of topical antiacne therapies.

**Adapalene + BPO**
- A novel once-daily acne treatment combining adapalene with BPO was US FDA-approved in January 2009.
- Multiple pathogenic factors are targeted. Adapalene modulates cellular differentiation, keratinization, and inflammation; BPO has bactericidal and keratolytic effects.

**Azelaic Acid**
- Due to its antibacterial, anti-inflammatory, keratolytic, and comedolytic effects, azelaic acid 15% gel has been used successfully alone or in combination with other medications to treat mild-to-moderate acne.
- It also reduces post-inflammatory hyperpigmentation, once acne lesions heal.

**Dapsone**
- Dapsone, an antibacterial agent, was US FDA-approved in 2008 for the treatment of moderate-to-severe acne.
- Studies with dapsone 5% gel showed significant reductions in acne lesions following 4 weeks of therapy.

The two primary areas identified in nonadherence include:
1. Difficulties with the patient-physician relationship (i.e., miscommunication, lack of dialogue, and patient misconception of benefits and risks of treatment).
   - The treatment plan, rate of improvement, and side-effects may be inadequately explained to patients.
   - Patients misunderstand physician instructions.
2. Treatment-related issues:
   - The most common reasons include forgetfulness, side-effects, did not feel the need, and inconvenience.
   - Adherence is also compromised by the lag time to visible effect, the complexity of treatment regimens, and the desire to incorporate cosmetics, such as foundations, moisturizers, and sunscreens.

Pharmacists are crucial advocates in communicating therapeutic objectives to patients, educating them on both acne and medications, and encouraging adherence through:
- reinforcing the aims of initial and long-term strategies.
- assisting to establish realistic treatment expectations, including clinically relevant improvement, which is approximately 4-6 weeks for most topical therapies.
- counselling on aggravating factors, proper medication use, and potential adverse effects.
- emphasizing to patients that overuse can amplify skin irritation and underuse can reduce product efficacy.
- understanding that even mild acne can have a profound emotional impact on affected patients.
- implementing the prescribing physician’s vehicle recommendations. In particular, avoiding substitution of the pump dispenser for the tube, in order to gain patient adherence and treatment satisfaction.

Tips for Acne Management
- Select aqueous over alcohol vehicles to reduce irritation.
- Frequency and duration of application may be adjusted to reduce the potential for dryness and irritation (e.g., initiate once-daily treatment after dinner; progressively increase duration as patient tolerance permits).
- Provide descriptive estimates of amounts to apply (e.g., pea-size amount of gel to each of the four facial regions: forehead, each cheek, central face).
- Advise patients to apply topical medications to the entire affected area and not just the acne lesions.
- Use simple skin care regimens:
  - Patients who do not use foundation or sunscreen can apply topical agents in the morning and evening.
  - If patients use foundation and sunblock, apply medication in the evening only or apply a clindamycin product with SPF 15 in the morning.
  - Suggest using gentle cleansers to avoid compounding irritation and dryness.
  - Recommend using non-comedogenic foundations, water-based cleansers, and oil-free moisturizers.

An interplay of multiple factors contributes to the successful outcome of topical acne treatment. The appropriate selection of medications and vehicles should be patient-specific and take into account efficacy, tolerability, and convenience, as well as individual preferences. Furthermore, pharmacologic initiatives aimed at optimizing acne management must be accompanied by patient education. Advances in topical acne formulations, active agents, and vehicles hold the promise of improved outcomes with reduced adverse effects, greater tolerability, and dosing simplicity.

References
Moisturizers: An Essential Component in Eczema Management

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Introduction

Atopic dermatitis (AD), or eczema, is a chronic, relapsing form of skin inflammation that is attributable to multiple pathogenic, genetic, and environmental factors, as well as to a dysfunctional epidermal barrier. Immune responses involved in AD culminate in dry skin, pruritus, and IgE mediated sensitization to food and environmental allergens. An improved understanding of crucial skin barrier defenses and the inflammatory cascade that drives the disease has led clinicians to reassess conventional approaches to treatment and recognize emollients for their therapeutic potential. Accordingly, emollient-based moisturizers and cleansers have been established as essential adjuvants for successful AD management.

Background

AD is very common.
- Prevalence is estimated at 15%-30% in children and 2%-10% in adults.
- In 85% of AD-afflicted children, onset of disease occurs before the age of 5 years.
- Up to 70% of children experience a spontaneous remission before adolescence.
AD is associated with a marked decrease in skin barrier function due to endogenous factors.
- Increasing evidence implicates one of the primary causes of AD as a genetic defect in the epidermis that permits the infiltration of allergens, environmental irritants, and microbes, thus inducing inflammatory responses.
- A defective skin barrier prohibits the necessary levels of antimicrobial peptides to form in the epidermis in order to protect against infectious agents, such as Staphylococcus aureus (S. aureus).

The Role of Moisturizers in Optimal AD Management

A persistent feature of AD is dry skin that is caused by a combination of intrinsic disease mechanisms and hyperreactivity to exogenous factors. Some treatments for AD can further exacerbate xerosis, itching, and irritation. Such external insults on an already impaired skin barrier drive the dry skin cycle and leave skin vulnerable to microbial infections. For these reasons, maintaining hydration and restoring epidermal barrier defenses provide the rationale for moisturization therapy.

What are Moisturizers?
- Moisturizers are composed of a combination of key ingredients that are categorized as emollients, humectants, and occlusives, which work synergistically to enhance hydration and barrier function.
- A randomized controlled study showed that well-designed formulations incorporating these constituents can improve the epidermal barrier function and increase skin hydration levels; however, the effects are determined by individual product composition.

How do Moisturizers Work?
- The mechanism of action of emollients may be elucidated as a role substitution by lipid ingredients, which take on the functions of naturally occurring lipids that are either absent or impaired in eczematous skin.
- Treatment of the skin with moisturizers can repair the skin barrier, increase water content, reduce transepidermal water loss (TEWL), and restore the lipid barriers’ ability to attract, retain, and redistribute water.
  - Maximum effects are derived from prophylactic and frequent use.
  - Moisturizers maintain hydration in the skin by slowing TEWL. In doing so, they help dry and/or aging skin to improve its structural integrity, appearance, and tactile properties.
- By covering tiny fissures in the skin and providing an occlusive protective film over the stratum corneum (SC), moisturizers restore the epidermal barrier and reduce the penetrability of allergens and irritants.

Moisturizers Demonstrate Adjuvant Properties
- Regimented moisturization has become standard adjunctive AD therapy by serving as a foundation to support pharmacologic measures, reducing the need for topical corticosteroids and calcineurin inhibitors, and mitigating the side-effects from medications.
- During flares, OTC combination preparations containing a moisturizer with a topical corticosteroid (e.g., clobetasone and hydrocortisone) are helpful to control inflammation and restore the skin barrier.
Emollients
- Emollients are mainly lipids and oils that hydrate and improve the appearance of the skin by contributing to softness, smoothness, and improved flexibility (Table 1).
  - The lubricity of some moisturizers can influence consumer satisfaction and product preference.
  - The SC of AD patients have significantly reduced levels of ceramides (lipid molecules), which are important components of skin structure.
  - The topical replacement of lipids serves to ‘fill the cracks’ between clusters of desquamating corneocytes.

Humectants
- Humectants attract and retain hydration in the skin by enhancing water absorption from the dermis into the epidermis, or by absorbing water from the external environment (Table 2).
  - Many humectants also have emollient-like properties.7
  - The most effective humectant is the trihydroxylated molecule, glycerin, which is also commonly referred to as glycerol.
  - Glycerin is the most widely used humectant.

- A double-blind study comparing glycerin with urea showed that although both compounds were equally effective in treating xerosis, glycerin caused significantly less adverse skin reactions.8
- Urea is another commonly used humectant that is effective against TEWL.
- Avoid the use of urea-containing moisturizers in young children due to irritation.

Occlusives
- Occlusives reduce TEWL by creating a hydrophobic barrier over the skin and contributing to the matrix between corneocytes (Table 3).
  - Efficacy is enhanced when occlusives are applied to slightly dampened skin.
  - Their main limitations include odour, potential allergenicity, and a ‘greasy’ feel.
  - Petroleum jelly (petrolatum), in a minimum concentration of 5%, is the most effective occlusive, followed by lanolin, mineral oil, and silicones.
  - Silicone-based derivatives (e.g., dimethicone) are oil-free alternatives that are noncomedogenic, nonirritating, nonsensitizing, and more cosmetically acceptable.

### Table 1. Common substances with emollient properties

<table>
<thead>
<tr>
<th>Types of Emollients</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astringent emollients</td>
<td>Cyclomethicone, dimethicone, isopropyl myristate, octyl octanoate</td>
</tr>
<tr>
<td>Dry emollients</td>
<td>Decyl oleate, isopropyl palmitate, isostearyl alcohol</td>
</tr>
<tr>
<td>Fattening emollients</td>
<td>Castor oil, glycercyl stearate, jojoba oil, octyl stearate, propylene glycol</td>
</tr>
<tr>
<td>Protective emollients</td>
<td>Diisopropyl dilinoleate, isopropyl isostearate</td>
</tr>
<tr>
<td>Protein rejuvenators</td>
<td>Collagen, elastin, keratin</td>
</tr>
</tbody>
</table>

### Table 2. Common substances with humectant properties

<table>
<thead>
<tr>
<th>Types of Occlusives</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatty acids</td>
<td>Lanolin acid, stearic acid</td>
</tr>
<tr>
<td>Fatty alcohols</td>
<td>Cetyl alcohol, lanolin alcohol, stearyl alcohol</td>
</tr>
<tr>
<td>Hydrocarbon oils/waxes</td>
<td>Caprylic/capric triglyderide, mineral oil, paraffin, petrolatum, silicone-derivatives (cyclomethicone, dimethicone), squalene</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>Lecithin</td>
</tr>
<tr>
<td>Polyhydric alcohols</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Sterols</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Vegetable waxes</td>
<td>Candelilla, carnauba</td>
</tr>
<tr>
<td>Wax esters</td>
<td>Beeswax, lanolin, stearyl stearate</td>
</tr>
</tbody>
</table>

### Table 3. Common substances with occlusive properties
**Recommendations for Use**

The following adapted guidelines for the use of moisturizers in AD, developed by the National Institute for Health and Clinical Excellence, serve as practical advice for patients and their health care providers.

- Patients should be offered a choice of unperfumed emollients:
  - suited to their individual needs and preferences.
  - for everyday moisturizing, as well as suggesting emollient-enriched washing and bathing formulations.
- Moisturizers should be:
  - used more often and in larger amounts than other treatments.
  - used even when AD is clear.
  - used while using other treatments.
  - offered as a single or combination product (offer alternatives if one formulation causes irritation or does not gain patient acceptance).
  - easy to apply throughout the day.
- Recommend leave-on moisturizers in large quantities.
- Instruct patients or their parents on sufficient and proper application.
- When multiple topical products are used concurrently, instruct patients to apply them one at a time, allowing for several minutes to pass in-between applications.
- Consider increasing the use of emollients if patients report difficulties in controlling itch.

**Mild Skin Cleansers**

The regular use of mild cleansers is an important aspect of optimal AD management. Not only is cleansing an essential part of basic hygiene, but it also removes dirt, sweat, bacteria, and exfoliated cells, which prepares the skin to receive topical medications and improves drug absorption.

- AD lesions are commonly colonized with *S. aureus*. Routine cleansing can enhance antimicrobial activity against *S. aureus* and decrease the chances of infection.
- Care must be taken to minimize any further weakening of the SC barrier during cleansing. The use of improper techniques and unsuitable cleansing agents on the face or body can initiate flares or exacerbate AD.
  - The use of anionic detergents (i.e., soaps) can alter the pH of skin, resulting in increased sensitivity to irritants and conditions that can promote bacterial proliferation.
  - While removing excess sebum, cleansers can also inadvertently damage intercellular lipids, which can lead to further impairment of the barrier function and cause dry skin.
- Cleansers that are suitable for eczematous skin are generally based on mild synthetic surfactants that cause minimal barrier disturbances.
  - Non-ionic surface-acting agents (e.g., silicone and polysorbate) are less likely to cause irritation and are pH-compatible with the skin.
  - Silicone surfactants, such as dimethicone, are effective at eliminating surface debris without completely stripping away protective oils.
  - Emollients contained in cleansers can minimize barrier damage by emulsifying dirt and oil for easy removal, while at the same time replacing lipids that are lost during the washing process.

**Additional Tips for AD Patients**

Pharmacists can be instrumental in reinforcing the aims of prescribed treatments, providing information on potential side-effects, and offering practical advice on sustainable, long-term management strategies.

- Instruct patients to apply topical medication as soon as AD symptoms appear and discontinue drug treatment once the skin inflammation resolves, in order to minimize side-effects.
- Explain that the associated adverse effects from topical steroids or calcineurin inhibitors are generally limited to long-term and/or overuse, but short-term or intermittent use are safe and efficacious.
- Stress the importance of routine maintenance therapy with fragrance-free moisturizers and mild cleansers.
The best practice management of AD must include patient education. Pharmacists are encouraged to provide verbal and written information on AD and selected treatments, as well as practical demonstrations of proper administration. Remembering the 4 Rs can help to simplify the multi-layered approach for management.

**Recognize**
- Recognize and diagnose the condition promptly in order for treatment to be initiated.
- AD patients have a predisposition for developing other atopic conditions, such as asthma and allergic rhinitis.⁴
- Encourage patients to maintain a diary to track foods eaten, flares, and the use of medications, moisturizers, and cleansers, which can guide therapeutic decision-making.

**Remove**
- Avoidance is a central AD management strategy. Identify and eliminate relevant triggers (e.g., irritants, aeroallergens, and foods) and seek ways to reduce stress.
- Mild cleanser use can help to remove surface dirt, irritants, and microbes.
- Consider allergy testing to identify triggers.

**Restore**
- The regimented use of emollients can partially repair and restore the skin barrier and reduce infections and allergic reactivity.
- Body washes incorporating nonirritating surfactants, emollients, and humectants can replenish barrier lipids during cleansing to minimize TEWL. Lukewarm baths (5-10 minutes in duration) are recommended over showers.
- Creams and ointments are more effective for eczematous skin. Apply moisturizers 3-5 minutes after bathing.

**Regulate**
- When flares occur, interrupt and regulate inflammatory responses with immediate treatment in order to break the itch-scratch cycle and limit AD severity.
- Therapeutic strategies include topical corticosteroids, topical calcineurin inhibitors, antimicrobials, and oral antihistamines, as well as routine skin care.
- In patients exhibiting an inadequate response to therapy, assess treatment adherence, side-effects, and review moisturizer and cleanser use.

**Conclusion**
Due to the chronicity of AD, as well as multiple factors contributing to its etiology, successful management requires a multipronged approach that includes lifestyle modifications, adaptations to skin care practices, and medical intervention. Although topical corticosteroids are firmly established as the cornerstone therapy, long-term and overuse are associated with skin atrophy and adverse systemic effects. The combination of moisturizers with topical steroids can have a significant steroid-sparing effect, especially in children with mild-to-moderate AD. A therapeutic approach that incorporates patient education and emollient therapy can complement pharmacologic measures to extend periods of remission and significantly lessen the disease burden.

**References**
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