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Clinical Evidence. Practical Advice

Editor-in-Chief: Dr. Stuart Maddin

Dr. Stuart Maddin, MD, FRCPC
EDITOR-IN-CHIEF

Dr. Stuart Maddin is the Chairman of SkinCareGuide. He is one of North America's leading dermatologists and the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the Clinical Trials Unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and World Health Organization (Geneva). He is the founder of the Dermatology Update symposia, now in its 29th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology – International League of Dermatological Societies.

Karen Yan, RPh, BScPharm
PHARMACIST ADVISOR

Karen is a registered pharmacist working in Vancouver, BC. She is a graduate from the Faculty of Pharmaceutical Sciences at the University of British Columbia. Karen has a keen interest in continuing pharmacy professional development. In addition, during her senior year of undergraduate studies, she participated in research and development in pharmaceutics. Presently, Karen works as a community pharmacist at Laurel Prescriptions, a pharmacy that specializes in parenteral and topical compounding.

Adjunctive Skin Care for Acne

Shannon Humphrey, MD, FRCPC, FAAD

Department of Dermatology and Skin Science,

University of British Columbia, Vancouver, BC, Canada

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.[1] Emerging evidence suggests that acne is associated with epidermal barrier impairments, including stratum corneum (SC) barrier permeability.[2] There is also mounting evidence to demonstrate an association between AV and inherent epidermal barrier dysfunction involving increased filaggrin expression and decreased ceramide levels.[2] 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:[3]
  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.[2]
- 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.[2]
- 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.[4]

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 BPO+adapalene (dose: BPO 2.5% + adapalene 0.1%) or BPO + clindamycin (available doses: clindamycin 1% + BPO 5%) for treatment of mild-moderate papulopustular acne.[5]
- Fixed-dose combination products reduce the number of medications and applications; therefore have potential to improve adherence.[6]
- Retinoids prevent and break down blackheads and also have anti-inflammatory activity.
- BPO is an antimicrobial agent that has some keratolytic effects and does not contribute to antibiotic resistance as it is bactericidal through an oxidative mechanism.

ALSO IN THIS ISSUE: **Androgenetic Alopecia: A Review of Topical Agents for Hair Growth Promotion** *(page 5)*

Acne Pathogenic Factors	Retinoids Adapalene Tazarotene Tretinoin	Benzoyl Peroxide	Antibiotics Erythromycin Clindamycin
Reduces production of sebum			
Targets *P. acnes*		X	X
Normalizes keratinization and desquamation	X	X	
Anti-inflammatory	X	X	X

Table 1: Topical acne therapies and their pathogenic targets

- 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).
- Combining a topical retinoid with a topical antimicrobial (BPO or topical/oral antibiotic) targets three pathogenic factors; trials show combination therapy results in significantly improved clearing as opposed to antimicrobial therapy alone.[6]

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.[4]

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.[7]
- A wide spectrum of skin cleansing agents exist for acne ranging from lipid free cleansers, syndets and astringents to exfoliants and abrasives.[8]
- 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.[9]
- 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, Effaclar, 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.[10]
- The different types of moisturizers include (Table 2):
  1. Occlusives
  2. Humectants
  3. Emollients
  4. Protein rejuvenators[11]
  5. Ceramides
- 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, nonacnegenic 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

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

Table 2: Types of moisturizers

being applied to the skin, decreasing the potential for skin sensitivity reactions.[10]

Acne Therapy & Adherence

- Treatment adherence in patients with AV is a significant problem and is documented at approximately 50%.[4]
- An estimated 30-40% of patients using topical acne treatment formulations do not comply with their prescribed regimen.[12]
- 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.[13]
- Additionally, novel delivery mechanisms and vehicles, such as pumps and foams, are convenient and preferred by patients, which may also improve adherence.[14]
- 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]

Treatment	Strategies
Topical therapy active	• Careful selection of topical therapy • Partially solubilized or micronized retinoid • Combination therapy to minimize irritation
Topical therapy vehicle	• Cream>gel • Hydrogel>alcohol gel • Excipients (humectants, emollients)
Application technique	• Applied to dry face every night with emollient • Consider alternate days • Consider short contact
Adjunctive skin care	• Gentle, non-comedogenic cleanser and emollient
Counselling	• Expectations • Application technique • Strategies to mitigate adverse events

Table 3: Strategies to improve treatment adherence

- 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 concomitantly with retinoid therapy could enhance treatment efficacy. Data from a randomized, splitface 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.[15] 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.[10] 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.[9]

Conclusion

Skin barrier impairment in patients with AV 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 AV and may improve patient tolerance to treatment.[2] 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.

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

Omar S. Shamsaldeen, MD[1] and Jerry Shapiro, MD, FRCPC[1,2,3]

[1]Department of Dermatology and Skin Science, The University of British Columbia, Vancouver, BC, Canada

[2]Vancouver Coastal Health Research Institute, The University of British Columbia, Vancouver, BC, Canada

[3]Department of Dermatology, New York University, New York, NY, USA

Introduction

Hair loss is a common dermatological problem that affects a large segment of the population both physically and psychologically. There are many causes of hair loss, such as telogen effluvium (thinning of hair as a result of hair follicles perpetually in a resting phase, as opposed to growth phase) and alopecia areata (an inherited autoimmune condition); androgenetic alopecia (AGA) also called male pattern hair loss (MPHL), is the most common. Hair loss can start anytime at or after puberty: many people have hair loss beginning in the late teens due to the effects of androgen hormones on hair follicles.[1] Its occurrence and severity increases with age, with at least 80% of Caucasian men displaying signs of MPHL by age 70.[2] Because of its considerable psychological impact, many patients seek treatment.[3] 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.[4]
- 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 growth phase duration and hair matrix volume.
  - In men, testosterone is the precursor to DHT. The conversion of T to DHT at the hair follicles is mediated by Type II 5α reductase enzyme.
- 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.

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.
- Telogen effluvium may present like early phase AGA.

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.[4]
- 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.[5,6] Further, it has been seen to prolong duration of anagen of the hair cycle, increase miniaturized hair follicle size, and preserve and thicken pre-existing hair.
- Data from a 16-week, randomized, double-blind, placebo controlled (RCT) study of the newly approved minoxidil 5% foam application showed at weeks 8, 12 and 16 the mean increase in target area hair count was significantly greater than placebo ($p<0.0001$).[7] 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).[7,8] 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.[7]
- 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.[9]
- 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.[4]

- 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.[8] The most frequently reported dermatological adverse events were erythema, rash, acne and pruritis. In long-term treatment, the most frequently reported nonserious adverse events were infection and accidental injury.[8]
- 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.[8]
- Increased hair shedding is possible in the first 2-6 weeks of treatment, which likely results from inducing anagen from the resting phase.[8] 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.[8]
- 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.[10]
- 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.[10]
- Systemic absorption of minoxidil is weak with only 0.3-4.5% reaching the circulation. It is excreted within four days.

Other Topical Agents

Prostoglandins

- 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.[11]

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.
- Ketaconazole's action on scalp microflora may benefit patients with AGA-associated follicular inflammation.[12,13]
- 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.[14]
- Further, ketoconazole decreases colonization of the skin by *Malassezia.*
- Ketoconaole also inhibits steroid synthesis and decreases DHT levels at the hair follicle by affecting androgen receptor activity.[14]

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.

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Skin Treatments Introduced in 2012

Type/Class of Therapy	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Acne	**CIP-Isotretinoin capsule** *Epuris*™ (in Canada) *Absorica*™ (in US) Cipher Pharmaceuticals	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.	Health Canada US FDA
Anesthetic	**Lidocaine 7% + tetracaine 7% cream** *Pliaglis*® Nuvo Research Inc. Galderma Laboratories	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.	Health Canada US FDA
Dupuytren's Contracture	**Collagenase clostridium histolyticum** *Xiaflex*® Actelion Pharmaceuticals Auxilium Pharmaceuticals	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.	Health Canada
Hereditary Angioedema	**C1 esterase inhibitor (human)** *Cinryze*® ViroPharma Incorporated	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.	Health Canada
Melanoma	**Ipilimumab** *Yervoy*™ Bristol-Myers Squibb	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.	Health Canada
	Vemurafenib tablets *Zelboraf*™ Genentech/Roche Group Plexxikon/Daiichi Sankyo Group	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.	European Commission Health Canada

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MohsSurgery.ca	PsoriasisGuide.ca	PsoriaticArthritisGuide.ca	RosaceaGuide.ca
SkinCancerGuide.ca	SkinCoverup.com	Sweating.ca	UnwantedFacialHair.ca

Medical professional sites:

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Social networking sites for patients and health care professionals:

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