

# Skin Therapy Letter<sup>®</sup>

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Editor-in-Chief: Dr. Stuart Maddin

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## Update on the Management of Actinic Keratoses

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### Introduction

Actinic keratoses (AKs), or solar keratoses, are pre-malignant cutaneous lesions that predominantly manifest in sun-exposed areas. They are one of the most common skin conditions seen by dermatologists, preceded only by acne vulgaris and dermatitis.<sup>1</sup> AKs are clinically relevant lesions due to their potential to evolve into invasive squamous cell carcinoma (SCC).<sup>2</sup> Additionally, they are considered a risk factor for the subsequent development of melanoma and non-melanoma skin cancer. There are numerous treatments available for managing AKs including those broadly categorized as destructive, topical field, and procedural field therapies. The recent introduction of imiquimod 3.75%, approved for the treatment AKs on the face and scalp, widens the therapeutic arsenal.

### Prevalence and Risk Factors

- In the northern hemisphere, it is estimated that between 11-25% of adults have at least one AK.<sup>3</sup>
- These lesions are most commonly seen in the older fair-skinned population or in individuals classified under Fitzpatrick skin phototypes I-III.
- Cumulative ultraviolet (UV) radiation exposure and older age are the most important contributing risk factors.
- Immunocompromised individuals or those with certain genetic syndromes (e.g., xeroderma pigmentosum and albinism) are at greater risk.

### Pathogenesis

- UV radiation is involved in the pathogenesis of AKs through inducing cellular DNA mutations in the skin, which may affect cell proliferation genes (e.g., p53 and ras) or prompt evasion of apoptosis.<sup>2</sup>
- Disruption of one of these genes may lead to formation of atypical keratinocytes in the basal layer and development of an AK; all of these histopathologic changes are limited to the epidermis.
- The absence of further UV light exposure may result in resolution through inherent repair mechanisms. However, additional UV light exposure may induce further DNA mutations resulting in the development of invasive SCC.

## Diagnostic Features

- AKs typically manifest as small (1-3mm), erythematous, scaly papules with a hyperkeratotic texture.
- They are best identified with touch rather than visual inspection alone.
- AKs are characteristically distributed in sun-exposed areas, including the face, bald scalp, ears, neck, anterior chest, dorsal forearms, and dorsal hands. Surrounding areas may show evidence of solar elastosis (e.g., telangiectasia, blotchy hyperpigmentation, and yellow discolouration of the skin).<sup>4</sup>
- The clinical variants of AKs include the cutaneous horn, lichen planus-like keratosis, pigmented actinic keratosis, and actinic cheilitis.<sup>4,5</sup>
- The natural history of AKs is variable and unpredictable; a lesion can follow one of three paths: it can persist, regress, or transform into an invasive SCC.
  - It is impossible to predict which path any given AK may take.
  - The risk of a single lesion progressing from an AK to a SCC ranges from 0.025-16% per year.<sup>6</sup>
- Over several years, these lesions can progress, becoming thicker and developing into a hypertrophic AK, Bowen's disease (SCC *in situ*), or an invasive SCC.
  - The stages of this biologic continuum are clinically indistinguishable, therefore, a biopsy should be performed if a SCC is suspected.
  - A presentation that includes pain, pruritus, induration, larger size, rapid growth, ulceration, bleeding, or resistance to treatment may point towards a more sinister pathology (i.e., SCC).<sup>4,5</sup>

## Treatment Overview

It is recommended that all AKs be treated, as there are no reliable clinical predictors to discern an AK from a SCC. If a SCC is missed, it may become locally invasive and destructive; these lesions are capable of metastases, resulting in death. Therapeutic choices are guided by efficacy, adverse effects, cosmetic results, and patient adherence.

## Destructive Therapy

The most common therapies for individual AKs work destructively by physically removing the lesion. These modalities should be considered first-line for isolated lesions or early presentations of AKs. Destructive therapies include liquid nitrogen cryotherapy, curettage with or without electrodesiccation, and shave excision. The main advantages of these procedures are that they are quick, procedurally simple, and provide adequate clearance of abnormal tissue.

### Cryotherapy

Cryotherapy is the most frequently utilized technique, with liquid nitrogen being the most commonly applied cryogen. Applying cryotherapy to the affected area lowers the skin to temperatures that destroy atypical AK cells.<sup>7</sup>

- This technique is ideal if lesions are scattered, limited in number, or for patients who are nonadherent to topical regimens.<sup>7</sup>
- Reported cure rates range from 39-83%.<sup>8</sup>
- Treatments are generally well-tolerated and do not require local anesthetic, but the procedure can be painful and result in permanent hypopigmentation.
- Potential side-effects include blisters, scarring, textural skin changes, infection, and hyperpigmentation.

### Curettage and Shave Excision

Curettage consists of using a curette to mechanically remove atypical cells. A shave excision using a surgical blade is another technique. These may be followed by electrocautery, which will destroy additional atypical cell layers, as well as provide hemostasis.

- These techniques are most appropriate for treating individual AKs, cases where a biopsy is required to rule out frank carcinoma, or for hypertrophic AKs that are refractory to other treatments.
- Potential side-effects include infection, scarring, and dyspigmentation, as well as anesthetic related side-effects.

## Topical Field Therapy

Commonly, physicians are faced with patients who are covered in actinic damage, a clinical scenario now described as field cancerization, which includes both clinical and subclinical lesions within a given anatomical region.<sup>9</sup> For these patients, a different therapeutic approach, known as field therapy, is needed for the clearance of both clinically visible and subclinical AKs within the treatment area.

### *Topical 5-fluorouracil (5-FU)*

The antimetabolite 5-FU was the first approved agent for topical field therapy. Discovered serendipitously when AKs were noted to become inflamed and subsequently resolved in patients receiving systemic 5-FU as a chemotherapeutic agent; it was eventually designed into an effective topical formulation. It acts as a thymidylate synthase inhibitor by blocking a methylation reaction, which in turn disrupts DNA and RNA synthesis and effectively stops the growth of the rapidly proliferating or cancerous cells.<sup>10</sup> As such, 5-FU preferentially targets the atypical cells over normal skin tissue.

- The average cure rate is 62.5%,<sup>11</sup> but for optimal results full patient adherence is necessary. Recommended dosing is twice-daily for 3 weeks.
- There is evidence showing concurrent treatment with topical tretinoin enhances the effectiveness of 5-FU.<sup>12</sup>
- It is common for all patients undergoing successful treatment with 5-FU to experience inflammation, erythema, and erosions.
- Common side-effects include pain, pruritus, photosensitivity, and burning at the site of application.
- 5-FU can worsen preexisting cutaneous conditions (e.g., melasma or acne rosacea), as such, use should be avoided in these patients.<sup>7</sup>

### *Diclofenac*

Diclofenac 3% gel is a nonsteroidal anti-inflammatory drug, which is believed to exert its effects through the inhibition of cyclooxygenase (COX), especially COX-2. The production of prostaglandins is thought to suppress the immune system, thereby allowing tumours to form.<sup>13</sup> Without COX, prostaglandin production is reduced and the cascade is disrupted.<sup>13</sup>

- Despite the more rigorous treatment regimen (twice daily for 90 days), only mild to moderate local skin reactions are noted.
- Though rare, drug-induced hepatotoxicity reports have surfaced, consequently transaminases should be measured periodically in patients on long-term therapy.

### *Imiquimod*

Topical 5% imiquimod cream was originally indicated as a treatment for genital and perianal warts; additional approved indications for treating AKs and superficial basal cell carcinomas followed. It is used off-label for Bowen's disease, invasive SCC, lentigo maligna, molluscum contagiosum, keloid scars, and others.<sup>14</sup> Imiquimod acts as a toll-like receptor-7 agonist, which results in modification of the immune response and stimulation of apoptosis, thereby disrupting tumour proliferation.<sup>15</sup> Stockfleth et al.<sup>16</sup> demonstrated that 84% of treated AKs showed clinical clearance with one 12-week cycle of 5% imiquimod therapy.

- Common localized irritation coupled with its long duration of treatment (twice-weekly for 16 weeks) can discourage patient adherence.
- Treatment should be applied to both the lesion and surrounding tissue to target subclinical AKs.
- Rare systemic effects include fatigue, flu-like symptoms, headaches, myalgias, and angioedema.

In December 2009, Health Canada approved the use of imiquimod 3.75% for the treatment of AKs on the face or balding scalp. Two identical placebo-controlled trials have evaluated the safety and efficacy of imiquimod 3.75%.<sup>17,18</sup>

- In the trial by Swanson et al.,<sup>17</sup> creams were applied daily to the entire face or balding scalp for two 2-week treatment cycles, separated by a 2-week interval without treatment.
  - Patients applying imiquimod 3.75% achieved a median lesion reduction of 82%, while just over one-third experienced complete clearance.
  - These efficacy data rival those achieved using imiquimod 5% twice-weekly for 16 weeks, but with the advantage of significantly improved patient tolerance.
  - Therapy was found to be safe and did not result in any serious adverse events.
  - Erythema was observed in most patients, with about 25% developing severe erythema. However, no patients withdrew from the study as a result of this.
    - Compliance rates were noted to be >90%.<sup>17,18</sup>
- Overall, the newly approved formulation of imiquimod 3.75% is a reasonable alternative to imiquimod 5%, as it demonstrated comparable efficacy, but with a much more simplified, shorter dosing regimen.
- Additionally, imiquimod 3.75% is approved for the treatment of a larger surface area of up to 200cm<sup>2</sup>, compared with 25cm<sup>2</sup> for the 5% formulation, and thus, is able to target more AKs.

## Procedural Field Therapy

Procedural field therapies may be an appropriate option for patients who require minimal down time, are unlikely to adhere to a topical approach, have AKs resistant to topical therapy, or favour an improved cosmetic result.

- Treatment options for procedural field therapy include photodynamic therapy, manual dermabrasion, laser resurfacing, cryopeeling, and chemical peels.
- Each of these techniques treats AKs by destroying the superficial layers of the skin through physical or chemical means.

### *Photodynamic Therapy (PDT)*

PDT is a procedural field therapy that utilizes topical 5-aminolevulinic acid (ALA) or methyl aminolevulinate to target AKs. These molecules preferentially find their way

into the hyperproliferating cells, which lack normal cell to cell adhesion junctions, and are converted intracellularly to protoporphyrin IX (PpIX).<sup>19</sup> This photosensitizer is then exposed to blue or red light, which corresponds to the peaks in the absorption spectrum of PpIX, resulting in a phototoxic reaction that destroys the abnormal cell.<sup>19</sup>

- PDT is effective for the treatment of multiple and diffuse AKs, and the cosmetic results are generally excellent.
- PDT is not suited for treating thicker or deeper AKs<sup>19</sup> and is generally reserved for patients who exhibit an inadequate response to topical field therapy or cryosurgery.
- Patients may experience erythema, edema, and a burning sensation during therapy.

## Conclusion

There is no widely accepted algorithm for the treatment of AKs. Often several different treatment regimens must be employed to manage AKs, especially with widespread or resistant cases. As always, the best way to manage AKs is prevention by avoiding exposure to significant or unnecessary UV radiation. Family physicians can play an important role in encouraging patients to wear broad-based sunscreens, wide-brimmed hat, protective eyewear, and avoiding the sun during peak hours, which may prevent recurrence or limit the progression of AKs. Furthermore, patients are well-served by offering education on the potential side-effects and expected onset of action of topical field therapies.

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# Male Skin Care

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## Introduction

For decades, skin care has primarily been considered to be the domain of women, but recently, an increasing number of men are also endeavouring to maintain optimal skin health and prevent unwanted changes that can occur with intrinsic and extrinsic aging. Caring for the skin requires a basic understanding of its functions and the differences between genders, as well as variations among individuals. Although some skin care products can be effectively used by both men and women, awareness of gender-specific attributes are helpful for guiding aspects of skin care regimens and the choice of products, in order to improve outcomes. This article will focus on the unique facets of men's skin physiology with particular emphasis on shaving and the treatment of pseudofolliculitis barbae.

## Overview of Differences in Men

The skin provides the interface between the body's internal and external environments. As the largest organ in the body, its complex functions include temperature regulation, biochemical and immune defence against microorganisms, buffering and protection of internal organs, as well as sensation (in relation to physical and social interactions). Among other factors, the skin of men and women differs as a consequence of hormonal influences. Herein, some male-specific physiologic features (Table 1) related to skin are described.

**Hair:** Although hair does not perform a vital function, its importance in self-perception and social interactions is considerable. All hair follicles form before birth and later respond to hormonal influences.

- Hair distribution and characteristics differ between genders and are largely determined by a combination of genetic, cultural, interpersonal, and behavioural factors.
- During adolescence, under the influence of sex hormones (e.g., testosterone), vellus hairs of androgen-sensitive areas (facial, pubic, and axillary regions) mature to terminal hair follicles.
- In addition to stimulating hair growth, the rise in testosterone levels in males increases the size, growth

rate, and pigmentation of hair. As such, men have more facial hair than women, making this attribute one of the most defining features of males.<sup>1</sup>

**Sebaceous glands:** Sebaceous glands (SGs) are associated with hair follicles throughout the body, with the face and scalp having the highest density. Oily secretions (sebum) from SGs are thought to influence stratum corneum hydration and lubrication, as well as provide protection from microorganisms.

- SGs are regulated by androgens, resulting in increased size and secretory activity.
- Typically, men produce more sebum than women, therefore, severe acne and subsequent potential sequela of acne scarring are more prevalent in men than in women.<sup>1,2</sup>

**Skin thickness:** Skin thickness reflects the composition of epidermis and dermis; collagen, ground substance, water, and elastic fibers contribute to skin thickness.

- At all ages, male skin is thicker than that of females in all anatomic areas, but onset of skin thinning can occur as early as 20 years of age.<sup>1-3</sup>
- In contrast, women's skin, although thinner, maintains its thickness until about the fourth or fifth decades of life.

Condition/Characteristic	Description of Male-prominent Features
Hair distribution	Men's facial hair is thicker and grows faster
Sebaceous glands	Men have higher sebum secretion
Skin thickness	At all ages, men's skin is thicker
Sweating	Men have a higher sweat rate
Immunity	Testosterone tends to inhibit the immune system, whereas estrogen acts as a stimulant
Wound healing	At all ages, men have slower wound healing rates
Skin cancer	Men are more prone to skin cancer

**Table 1:** Physiologic attributes of men in comparison to women

## Overview of Differences in Men (continued)

**Sweating:** Sweat, an odourless liquid, is produced by eccrine and apocrine glands. Eccrine glands are distributed throughout the body except at the mucous membranes. Apocrine glands are localized in the axillae, areolae, and in the perineal regions.

- Men have a higher sweat rate than women.<sup>1</sup>
- In comparison with men, sweating is triggered at higher body temperatures before perspiration occurs in women.
- Consistently warm conditions, especially in the underarm regions, encourage bacterial growth that causes body odours. Particularly in males, increased hair density in these areas helps to control moisture. The regimented use of antiperspirants or deodorants can also assist in reducing and managing perspiration and/or odours.

**Immunity:** Based on intricate processes, testosterone generally inhibits the immune system, whereas estrogen stimulates it.

- Men have a greater predisposition to bacterial and viral infections, and therefore, recovery from internal infections may present more challenges.<sup>1,3</sup>

**Wound healing:** Animal studies indicate that male rat fetuses experience slower rates of epidermal barrier formation in comparison with females. Improved cutaneous wound healing was observed when male mice were castrated, decreasing the influence of androgens.

- At all ages, men appear to have slower wound healing rates than women<sup>1,3</sup> and are at greater risk for dysregulated wound healing, which is particularly evident in the elderly population.

**Skin cancer:** Men may have greater susceptibility to skin cancer. More specifically, squamous cell carcinoma and basal cell carcinoma are more commonly diagnosed in males.<sup>1,3</sup> In addition, men have higher mortality rates from melanoma, when compared with women.

- Behavioural aspects of men's lives, as well as gender distinctions in immunity, may explain these differences.
- Consequently, the need for adequate sun protective strategies and annual skin check-ups should be reinforced across all at-risk patient populations.

## Shaving

Facial hair removal practices adopted by men and women can differ significantly. Women prefer manual razors, waxing, threading, electrolysis, or the use of depilatories; whereas men favour the use of manual or electric razors to manage facial hair growth.<sup>4</sup> The shaving ritual is individualistic and focused on easing the associated discomfort. As such, the goal of shaving products should be to improve the process by increasing the closeness of the shave and avoid causing redness, dryness, and ingrown hairs. The optimal shave should be fast, comfortable (minimizing irritation, nick/cuts, and razor burns), effective (e.g., achieving desired results and restoring smoother skin post-shave with moisturizers), and safe (e.g., without aggravating or causing more skin problems, such as redness, infection, and ingrown hairs).

The key components of successful shaving include:

1. **Pre-shave:** In this phase, the hair and skin need to be prepared for shaving. It is important to cleanse the face of pollutants, dirt, and contaminants by using lukewarm water and mild soap. This is followed by application of shaving lubricant (e.g., creams or gels). This step serves to moisten the skin and hairs, making them softer and easier to cut; a dry razor shave is difficult to achieve without aggravating the skin and causing razor burn. Although adequate hydration time allows for easy hair cutting, excess hydration can weaken the skin, making it more vulnerable to damage (i.e., insufficient hydration will leave hair too rigid and excessive hydration will leave skin too soft to withstand contact with the blade). Furthermore, shaving lubricants assist in reducing friction between the skin and the shaving blade, allowing for an easier glide of strokes. The shaving preparation should not aggravate the skin or cause undesirable effects, such as worsening of acne or induce an allergic reaction. Other properties, such as a mild anesthetic effect (minimizing pain and razor burn), scent, as well as texture, may enhance product appeal.
2. **Shave:** The many different blade-shaving technologies include single- and multiple-blade systems, which are further diversified by manual or electric operation. The basic design premise of multi-blade systems is that it produces a smoother shave in fewer strokes. Less passes improves shaving efficiency and causes less trauma to softened skin. These devices should also allow for full facial as well as neck shaving, while maintaining flexibility in order to access hard-to-reach areas, such as the cleft chin, corners of the mouth, and the region under the nose. The blades should meet quality standards, as imperfections in the free edge can damage skin and even cause scarring. Disposable razors or blade cartridges should be frequently inspected and replaced regularly depending on frequency of use to minimize the chance for cuts, irritation, and infection.

## Shaving (continued)

3. **Post-shave:** Once the actual shaving is completed, it is essential to restore hydration to just-shaved areas. During the shaving process, the outermost layer of the skin can be removed with the razor blade, resulting in decreased barrier function as well as micro-trauma to the skin, causing dryness and irritation. Moisturization and protection may be restored through the use of non-irritating, emollient enriched aftershave products that do not leave a greasy feel.

## Pseudofolliculitis Barbae

Pseudofolliculitis barbae (PFB) (razor bumps) is a common chronic inflammatory, non-infectious condition affecting both men and women; a male preponderance is seen in individuals with coarse or curly hair who shave. PFB frequently results from the habitual removal of unwanted hair, which promotes hairs to enter the dermis or epidermis prior to exiting the follicular opening (trans-follicular penetration) or re-entering skin that is adjacent to the follicular opening (extra-follicular penetration).<sup>5,6</sup> The use of inappropriate shaving techniques or devices that tug and pull at the skin, such as a dry and/or close shave (e.g., when pulling the skin taut) can promote trans-follicular penetration. Dry shaves create sharper hair tips and when a close shave is achieved, hair retracts into the follicle, creating conditions for penetration of the follicular wall by the regrown hair. Adequate pre-shave preparation and post-shave use of hydrating emollients can contribute to skin barrier maintenance and reduce the incidence of PFB.

The treatment of PFB should be centered on several key aspects:

- **Education:** Patients need to be well informed as to the causes of PFB with respect to unwanted hair removal and shaving practices.
- **Treatment:** It is essential to minimize trans-follicular penetration and extra-follicular penetration. As such, the hair should be left extended slightly (0.5mm to 1mm) above the follicular opening. Initially, growing a full beard is advisable to decrease the acute inflammation that is present during the active phase of PFB. Subsequently, shave hairs with the aid of a spacer (protects up to 1mm of hair from being cut), then the use of chemical depilatories or laser hair removal may be advisable.<sup>4,7</sup>
- **Goal:** Reinforce the message to patients that the benefits from following a balanced, healthy lifestyle outweigh the pursuit of managing physical imperfections.
- **Prognosis:** The desired improvement can only be achieved with persistence and focus on avoiding aggravating factors. Over time, repetitive skin trauma can cause papules and pustules to form, further progressing to keloid scars that appear as hard hyperpigmented bumps. The persistent pattern of hair removal practices, as well as patient dissatisfaction with their appearance, can lead to substantial psychosocial distress.

## Conclusion

The Dermatology Review Panel™ (DRP) seal of recommendation program is aimed at assessing the quality of evidence supporting OTC skin care product claims. Products are evaluated by an independent panel of Canadian dermatologists and approved submissions are granted the use of the DRP seal, which is intended to promote consumer education and assist in deciphering the validity of product claims.

As more manufactures are responding to the growing demand for men's skin care products and services, it is helpful for clinicians to be aware of the unique properties of male skin physiology, especially when patients seek advice prior to the implementation of therapeutic and cosmetic approaches. In particular, facial skin differs greatly between genders. In contemporary culture, shaving has evolved into a common, often necessary, ritual. With that in mind, acquiring a basic understanding of the complexities of men's skin better positions physicians to encourage patients to adopt optimal grooming strategies for shaving and skin care in order to avoid inflicting skin damage that can cause other complications, such as pseudofolliculitis barbae, allergenicity, hyperpigmentation, or even permanent scarring.

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