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Review Article

# Comparison of the Treatment Guidelines for Actinic Keratosis: A Critical Appraisal and Review

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Canadian Dermatology Association
Association canadienne de dermatologie

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## Abstract

There are currently several reputable guidelines on the treatment of actinic keratosis (AK) from groups in Canada, the United Kingdom, and Europe. These recommendations, based on evidence or expert consensus, offer clinicians a variety of treatment options for the different clinical presentations of AKs. Although the guidelines are similar in some regards, variations exist in treatment options, duration, and strength of recommendation. Some guidelines also lack input on specific therapies and certain types of AK, such as hypertrophic or thin presentations. The purpose of this article is to review and compare guidelines published by Canadian, UK, and European groups for the management of AKs in patients.

## Keywords

actinic keratosis, actinic keratoses, solar keratosis, guidelines, treatment, comparison

Actinic keratoses (AKs), or solar keratoses, are cutaneous lesions that present on photo-exposed sites such as face, scalp, neck, and extremities. They typically appear as small (3-6 mm), erythematous, scaly papules and are detected by palpation due to their rough texture.[1] When necessary, AKs can also be diagnosed histopathologically with characteristic dysplastic keratinocytes and irregular hyperchromatic nuclei.[2] This disorganised growth has been shown to progress to squamous cell carcinoma (SCC) in some cases, but it is difficult to predict which AK lesions will progress to SCC.[3] Thus, early diagnosis and treatment are appropriate for preventing progression to SCC.

Currently, several options for the treatment of AKs depend on a combination of clinical and patient factors. Treatment can be lesion directed (targeted therapy), field directed (for multiple lesions over large surface), or a combination of both.[4] Available options include field therapies (5-fluorouracil [5-FU] cream, diclofenac gel, imiquimod cream, ingenol mebutate gel) or destructive therapies (cryotherapy, curettage, chemical peel, dermabrasion, excision, photodynamic therapy [PDT], or laser resurfacing).[3-6] As no universal standard has been established for treatment, several working groups have developed their own guidelines for the management of AKs.[4] Despite the existence of numerous guidelines, there has been limited investigation into their overall quality. For instance, existing guidelines may diverge on management recommendations or are lacking in detail.[6] Factors such as availability of the treatment, adequacy of the evidence and literature search, type of studies incorporated, and author biases can also affect the generalizability of a guideline.[7] As different study methods were used in the production of each guideline, variations between guidelines may be present. The objective of our review is to summarise the current Canadian, European, and British guidelines and provide classification of their quality through an evidence rating scale.

## Methods

We completed a critical literature review comparing current Canadian, European, and British guidelines. A literature search of PubMed and EMBASE was conducted to identify relevant supporting studies, including randomised controlled trials, systematic reviews, and meta-analyses. Search terms included *actinic keratosis* or *solar keratosis* and relevant treatment modalities (such as cryotherapy, surgical excision, laser, photodynamic therapy, 5-FU, imiquimod, or ingenol mebutate). To identify any grey literature, we completed a search of Google and Google Scholar for additional relevant

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reports and conference abstracts. Guideline data were extracted into tabular format by R.B. and triple checked (by R.B. and S.Z.) for accuracy.

## Discussion

Guidelines for destructive and field therapies are highlighted in Tables 1 and 2. Special cases of AK and their management are outlined in Table 3. Available and unavailable treatments for each region are outlined in Table 4.

### Destructive Therapies

*Cryotherapy.* According to Canadian guidelines, cryotherapy with liquid nitrogen is currently the most common approach to management of isolated AKs.[1] Although UK guidelines also recommend extensive cryosurgery ('cryopeeling') as a field treatment, this is in contrast to the European and Canadian guidelines, which showed weak support for its extensive use.[1,5,8] One study has shown cryopeeling to be twice as effective as 5-FU when measured 1 to 3 years postoperatively, with superiority in terms of cost, availability, and healing time.[9] However, other studies reported 5-FU and other topicals to have more sustained clearance than cryotherapy.[1,10] These incongruences may be due to a lack of research on the cryopeeling process, which is operator dependant due to variations in freezing time and technique.[11]

*Surgical excision.* Although solitary AKs are not typically excised, surgical excision is recommended in cases of diagnostic uncertainty or lesions refractory to treatment.[1,5] In such cases, biopsy may be required for definitive histopathologic diagnosis and to rule out progression to invasive SCC.[8] Curettage is often recommended for hypertrophic AKs to debride lesions prior to applying other therapy, but curettage is limited when assessing dermal invasion.[5,12] There are currently no randomised controlled trials of surgical excision for AKs.[5] The general consensus among guidelines is for its use as a diagnostic tool.

*PDT.* Photodynamic therapy is recommended for the treatment of AKs that are superficial and diffuse or located at sites of poor healing.[5] For thicker AKs, more sessions of PDT may need to be given or AKs are pretreated with curettage to remove hyperkeratotic tissue before photosensitizing agents are applied.[1,5,8] The 2 PDT photosensitizing agents in use are aminolevulinic acid with blue light and methyl-aminolevulinate with red light.[3] In 5 randomised controlled trials, the patient response rates for around 2 cycles of PDT on face and scalp AKs ranged from 59.2% to 82% ($P \leq .0001$), with a 3-month follow-up.[13-17] When the creams are compared, 1 study of 15 patients found aminolevulinic acid and methyl-aminolevulinate both resulted in a significant reduction of AKs, but methyl-aminolevulinate was reported as less painful during and after light treatment.[18]

Compared with cryotherapy, PDT showed a similar clearance rate (69% PDT vs 75% cryotherapy, $P < .001$), with cryotherapy being more suitable for thicker lesions.[14] The cosmetic outcome of PDT was also rated higher than for cryotherapy.[14] Currently, PDT is recommended as the first-line treatment for patients with multiple AKs, according to an international consensus.[19]

*Laser resurfacing.* Laser resurfacing uses either carbon dioxide ($CO_2$) or erbium:yttrium aluminum garnet (Er:YAG). Since $CO_2$ laser is usually less painful and allows for faster wound healing, it is often preferred.[20] However, it is also noted that pain levels experienced may be contingent on the laser parameters and depth of treatment but not due to the laser modality itself. The Canadian and European guidelines suggest using laser resurfacing for areas of clustered AKs, with one application repeated several times.[1,8] Canadian guidelines have also mentioned laser resurfacing as an option in organ transplant patients.[1] However, there is limited evidence for the use of lasers, and UK guidelines describe it as a possible treatment in principle.[5]

Laser resurfacing appears to be more effective when combined with PDT than by itself. A randomised trial (n = 20) that compared PDT and $CO_2$ laser ablation (LA) alone found PDT to be superior in AK reduction and patient satisfaction (PDT, n = 12 [60%]; LA, n = 6 [30%]; equal preference, n = 2 [10%]).[20] Another trial using ablative fractional laser resurfacing (AFXL) has found it facilitates methyl-aminolevulinate uptake and improves PDT efficacy. AFXL-PDT had an 88% lesion response compared with 59% postconventional PDT ($P = .02$). These technique can be painful with more frequent pigmentary changes.[21]

*Other therapies.* Chemical peels were discussed in the Canadian and UK guidelines but not in European guidelines. The evidence for chemical peels is considered weak or poorly controlled, and accessibility is limited by the need for a specialist with experience in this procedure.[1,5] Medium-depth chemical peels have been compared with 5-FU and similar efficacy after 32 months, but both groups experienced an increase of AKs at 12 months for 25 to 75% of patients ($P = .039$).[22] This suggests that AKs might reappear, and long-term follow-up is necessary when using this treatment.

Only the UK guideline discussed dermabrasion for the face.[5] A retrospective case series of 23 patients found the prophylaxis time in patients who received dermabrasion lasted an average of 4 years, with 54% of patients developing another AK. Compared with chemical peels, cryotherapy, and 5-FU, dermabrasion was better long term. However, the complexity of the treatment and risk of blood splatter limit its use to centres with appropriate equipment.[23]

### Field Therapies

*5-FU.* The Canadian guidelines currently recommend using 5% 5-FU twice daily for up to 4 weeks as a treatment for

**Table 1.** Destructive Therapies Use in the Treatment of Actinic Keratoses.[a]

| Guideline | Canadian | United Kingdom | European |
|---|---|---|---|
| Cryotherapy | ▪ Most common approach to AK management.<br>▪ Used for isolated AKs as it is not effective as a field therapy. | ▪ Cryosurgery may be particularly effective for thicker lesions.<br>▪ Extensive cryosurgery over large areas (cryopeeling) can be used as a field treatment | ▪ Applied once, repeated up to several times. |
| Evidence and recommendation | Moderate evidence, strong recommendation. | Recommendation-A, quality of evidence-I | Provided for special cases in Table 3 |
| Surgical excision | ▪ AKs are not typically excised.<br>▪ However, solitary lesions can be excised (especially those resistant to treatment or new/recurrent lesions that require histologic diagnosis to rule out invasive SCC). | ▪ Unlikely to be first-line treatment unless there was diagnostic uncertainty. | ▪ Curettage: applied once, repeated up to 2 times.<br>▪ Biopsy is recommended when clinical diagnosis is unclear and/or when AK lesions are unresponsive to treatment. |
| Evidence and recommendation | No evidence, strong recommendation | No studies but a valuable tool | Provided for special cases in Table 3 |
| PDT | ▪ Two PDT systems are available for AK treatment: blue light with ALA and red light with MAL.<br>▪ Used for AKs found over large surface areas. Hyperkeratotic AKs are first treated with curettage before PDT.<br>▪ Curettage is generally required before PDT to remove hyperkeratotic tissue. | ▪ PDT using either ALA or MAL.<br>▪ PDT may be particularly effective for superficial and numerous confluent AKs or when lesions are located at sites of poor healing. | ▪ PDT using either ALA or MAL.<br>▪ Lesions are often pretreated prior to PDT (with curettage/topical intervention). |
| Evidence and recommendation | Provided for special cases in Table 3 | Recommendation A, quality of evidence I | Provided for special cases in Table 3 |
| Laser resurfacing | ▪ Can be used for areas with clustered AKs. | ▪ Carbon dioxide laser/other destructive energy.<br>▪ Laser not considered a good choice for any circumstance other than treating field disease. | ▪ Carbon dioxide laser: applied once, repeated up to several times.<br>▪ Er:YAG laser: applied once, repeated up to several times. |
| Evidence and recommendation | Provided for special cases in Table 3 | Recommendation B, quality of evidence I | Provided for special cases in Table 3 |
| Other | ▪ Medium depth chemical peels.<br>**the treatment details (%/dose, frequency, indications etc) were not specified for this.* | ▪ Chemical peels (TCA combined with 70% glycolic acid, phenol 100%).<br>▪ Dermabrasion (with silicon carbide sandpaper). | ▪ No other destructive treatments addressed. |
| Evidence and recommendation | | Recommendation B, quality of evidence I | |

AK, actinic keratosis; ALA, 5-aminolevulinic acid; MAL, methyl-aminolevulinate; PDT, photodynamic therapy; SCC, squamous cell carcinoma; TCA, trichloroacetic acid.
[a]Canada: Strength of recommendations based on Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. British: Based on the British Association of Dermatologists (BAD) Therapy Guidelines and Audit Subcommittee. Europe: GRADE system was used to assign strength to recommendations.

**Table 2.** Field Therapies Use in the Treatment of Actinic Keratoses.

| Guideline | Canadian | United Kingdom | European |
|---|---|---|---|
| 5-FU | ▪ 5% 5-FU can be applied twice daily for up to 4 weeks. | ▪ 5% 5-FU used twice daily for 3 to 4 weeks. | ▪ 0.5% 5-FU: once daily for 1 to 4 weeks.<br>▪ 5% 5-FU: once or twice daily for 2 to 4 weeks. |
| Evidence and recommendation | Provided for special cases in Table 3 | Recommendation-A, quality of evidence-I | Provided for special cases in Table 3 |
| Imiquimod | ▪ 5% cream applied 3 times a week over 4 treatment cycles.<br>▪ Daily application of 3.75% cream to the face/scalp for two 2-week cycles separated by a 2-week rest period. | ▪ 5% imiquimod cream is licensed for clinically typical, nonhyperkeratotic, nonhypertrophic AKs on face or scalp in immunocompetent adults if size or number of lesions limits the efficacy or acceptability of cryotherapy.[a]<br>▪ Applied at night and washed off in morning 8 hours later. Courses are 3 times/week for 4 weeks. Can be repeated for a further 4 weeks if needed.[a]<br>▪ Also available in a 3.75% cream for AKs of the head and scalp, applied once daily for two 2-week periods separated by 2 weeks.[b] | ▪ 2.5% imiquimod: once-daily application for 2 weeks followed by rest period of 2 weeks (with 1 or 2 treatment cycles).<br>▪ 3.75% imiquimod: once-daily application for 2 weeks followed by rest period of 2 weeks (with 1 or 2 treatment cycles).<br>▪ 5% imiquimod: once-daily application for 2 to 3 days/week for 4 to 16 weeks (continuously or intermittently). |
| Evidence and recommendation | Provided for special cases in Table 3 | [a]Recommendation A, quality of evidence I<br>[b]Recommendation B, quality of evidence I | Provided for special cases in Table 3 |
| Ingenol Mebutate | ▪ 0.015% for the face/scalp. Applied once daily for 3 days.<br>▪ 0.05% for trunk/extremities. Applied on 2 consecutive days. | ▪ 0.015% for face and scalp.<br>▪ 0.05% for limbs and trunk. | ▪ 0.015% for face/scalp: once-daily application for 3 days.<br>▪ 0.05% for trunk/extremities: once-daily application for 2 days. |
| Evidence and recommendation | Provided for special cases in Table 3 | Recommendation A, quality of evidence I | Provided for special cases in Table 3 |
| Other topicals | ▪ While mentioned as another potential topical treatment, diclofenac is not currently available in Canada. | ▪ Emollients are a reasonable option for mild AKs.[c]<br>▪ 3% Diclofenac gel is licensed for twice-daily application for 60 to 90 days.[a]<br>▪ Salicylic acid 50% in croton oil has been described as a treatment in combination with TCA 20% and pretreatment with topical tretinoin as a serial regimen for facial peel.[d]<br>▪ Pretreatment with salicylic acid 5% or 10% salicylic acid as a keratolytic in combination with 0.5% 5-FU has shown efficacy.[d] | ▪ 0.5% 5-FU + 10% salicylic acid: once-daily application for 6 to 12 weeks.<br>▪ 3% diclofenac (in 2.5% hyaluronic acid gel): twice-daily application for 60 to 90 days. |
| Evidence and recommendation | | [c]Recommendation B, quality of evidence II<br>[d]Recommendation A, quality of evidence III | Provided for special cases in Table 3 |

AK, actinic keratosis; 5-FU, 5-fluorouracil; TCA, trichloroacetic acid.

**Table 3.** Special Considerations Use in the Treatment of Actinic Keratoses.

| Guidelines | Canadian | United Kingdom | European |
|---|---|---|---|
| Single AK | ▪ Cryosurgery or surgical excision (Moderate evidence)[a]<br>▪ Other therapeutic options include<br>○ 5-FU (Moderate evidence)[b]<br>○ Imiquimod (High evidence)[a]<br>○ Ingenol mebutate (High evidence)[a] | ▪ **Good treatments:** cryosurgery, 5-FU, 5-FU + salicylic acid<br>▪ **Treatments that can be used:** diclofenac, imiquimod, ingenol mebutate<br>▪ **Rarely used:** curettage, PDT[d] | ▪ Cryotherapy (Evidence = 8.2/4.2)[a]<br>▪ Other therapeutic options include curettage (hyperkeratotic lesion), 0.5% 5-FU, 5% 5-FU, 0.5% 5-FU + 10% salicylic acid (hyperkeratotic lesion), 3.75% imiquimod, 5% imiquimod, ingenol mebutate, PDT[e] |
| Thin AK | ▪ Not addressed | ▪ **Good treatments:** 5-FU, 5-FU + salicylic acid<br>▪ **Fair treatments:** cryosurgery, diclofenac, imiquimod, ingenol mebutate, PDT<br>▪ **Rarely used:** curettage[d] | ▪ Not addressed |
| Hypertrophic AK | ▪ Curettage used alone/in conjunction with shave excision, electrodessication, or cryosurgery (Moderate evidence)[a] | ▪ **Good treatments:** curettage<br>▪ **Treatments that can be used:** cryosurgery, surgical excision, 5-FU + salicylic acid<br>▪ **Rarely used:** 5-FU, diclofenac, imiquimod, ingenol mebutate, PDT[d] | ▪ Curettage<br>▪ 0.5% 5-FU + 10% salicylic acid[e] |
| Multiple AK | ▪ Field therapies should be used:<br>○ 5-FU (Low evidence)[b]<br>○ Imiquimod (High evidence)[a]<br>○ Ingenol mebutate (High evidence)[a]<br>○ PDT (High evidence)[a]<br>○ Laser resurfacing (Low evidence)[b]<br>○ Medium-depth chemical peel (Low evidence)[b] | ▪ **Good treatments:** 5-FU<br>▪ **Fair treatments:** 5-FU + salicylic acid, cryosurgery, diclofenac, imiquimod, ingenol mebutate, PDT<br>▪ **Rarely used:** curettage[d] | ▪ 0.5% 5-FU (Evidence = 8.5/4.5)[a]<br>▪ 3.75% imiquimod (Evidence = 8.8/4.8)[a]<br>▪ Ingenol mebutate (Evidence = 8.1/4.1)[a]<br>▪ PDT + ALA (Evidence = 8.11/4.11)[a]<br>▪ PDT + MAL (Evidence = 8.12/4.12)[a]<br>▪ Other therapeutic options include cryotherapy, diclofenac, 5% 5-FU, 0.5% 5-FU + 10% salicylic acid (hyperkeratotic lesions), 5% imiquimod, 2.5% imiquimod, lasers[e] |
| Organ transplant patients | ▪ Field-directed therapies should be used to prevent AKs and nonmelanoma skin cancer:<br>○ Imiquimod (Low evidence)[a]<br>○ Ingenol mebutate (No evidence)[b]<br>○ PDT (Moderate evidence)[a]<br>▪ Other modalities that have been used include 5-FU, laser resurfacing, and medium-depth chemical peels[c]<br>▪ Biopsy/excise lesions that do not respond to treatment (No evidence)[a] | ▪ Treatment options not well addressed except to say that low-dose acitretin cream/systemic retinoids can be given to patients with multiple dysplastic skin lesions<br>▪ Capecitabine has shown reduction in monthly incidence of extensive AK (Recommendation C, quality of evidence II)<br>▪ Treatment for AKs in transplant patients are likely less effective compared with the general population | ▪ For single/multiple discrete lesions: cryotherapy (Evidence = 8.2/4.2)[a]<br>▪ PDT + ALA (Evidence = 8.11/4.11)[a]<br>▪ PDT + MAL (Evidence = 8.12/4.12)[a]<br>▪ For discrete hyperkeratotic lesions: curettage, 5% 5-FU, 5% imiquimod, lasers[e] |

AK, actinic keratosis; ALA, 5-aminolevulinic acid; 5-FU, 5-fluorouracil; MAL, methyl-aminolevulinate; PDT, photodynamic therapy.
[a]Strong recommendation.
[b]Weak recommendation.
[c]Level of evidence and strength of recommendation not specified.
[d]Evidence and recommendation provided for individual treatment modalities in Tables 1 and 2.
[e]All have weak recommendations

**Table 4.** Available and Unavailable Treatments for Actinic Keratoses.

| Region | Available Treatments | Not Covered by Guideline or Unavailable |
|---|---|---|
| Canada | **Destructive Therapies**<br>• Cryotherapy<br>• Surgical excision<br>• PDT (ALA, MAL)<br>• Laser resurfacing<br>• Medium-depth chemical peel<br>**Field Therapies**<br>• 5% 5-FU<br>• 5%, 3.75% imiquimod<br>• 0.015%, 0.05% ingenol mebutate<br>**Organ Transplant**<br>• See options above<br>• Acitretin | **Destructive Therapies**<br>• Dermabrasion<br>**Field Therapies**<br>• Diclofenac (unavailable)<br>• 0.5% 5-FU, 0.5% 5-FU + 10% salicylic acid (unavailable)<br>**Organ Transplant**<br>• Capecitabine |
| United Kingdom | **Destructive Therapies**<br>• Cryotherapy<br>• Surgical excision<br>• PDT (ALA, MAL)<br>• Laser resurfacing<br>• Chemical peel (TCA + 70% glycolic acid, 100% phenol)<br>• Dermabrasion (silicon sandpaper)<br>**Field Therapies**<br>• 5% 5-FU, 0.5% 5-FU + 10% salicylic acid<br>• 3% diclofenac gel<br>• 5%, 3.75% imiquimod<br>• 0.015%, 0.05% ingenol mebutate<br>**Organ Transplant**<br>• See options above<br>• Acitretin<br>• Capecitabine | **Field Therapies**<br>• 2.5% imiquimod (unavailable) |
| Europe (except United Kingdom) | **Destructive Therapies**<br>• Cryotherapy<br>• Surgical Excision<br>• PDT (ALA, MAL)<br>• Laser resurfacing<br>**Field Therapies**<br>• 5%, 0.5% 5-FU, 0.5% 5-FU + 10% salicylic acid<br>• 3% diclofenac gel<br>• 2.5%, 3.75%, 5% imiquimod<br>• 0.015%, 0.05% ingenol mebutate<br>**Organ Transplant**<br>• See options above | **Destructive Therapies**<br>• Chemical peel<br>**Organ Transplant**<br>• Acitretin<br>• Capecitabine |

ALA, 5-aminolevulinic acid; 5-FU, 5-fluorouracil; MAL, methyl-aminolevulinate; PDT, photodynamic therapy; TCA, trichloroacetic acid.

discrete AKs. The frequency of application is restricted due to its erosive nature.[1] The UK guidelines also recommend the use of 5% 5-FU twice daily, but for 3 weeks, for similar reasons.[5,10] Although the lower strength formulation of 5-FU is not yet marketed in Canada,[1] European guidelines discuss the use of 0.5% 5-FU for once-daily application over 1 to 4 weeks. The use of 5% 5-FU is also described for once- or twice-daily application over 2 to 4 weeks, which is consistent with the other guidelines.[8]

A systematic review of 13 RCTs (n = 864) examining the efficacy of 5-FU suggests that an overall 80% reduction in lesion count can be expected with about half the patients experiencing complete clearance. As similarly reported with the Canadian and European guidelines, this review also found that the quality of evidence is poor with limited studies on comparisons between 5-FU and alternatives.[24] One meta-analysis comparing 5-FU to 5% imiquimod was found, which inferred imiquimod's superiority in a complete response rate of 70.8% vs 52.2%.[25]

*Imiquimod.* In Canada and the United Kingdom, 5% and 3.75% imiquimod are used. The 5% imiquimod has a dosing cycle of 3 times a week over a 4-week treatment cycle, and the 3.75% formulation is used daily over two 2-week cycles

separated by a 2-week rest.[1,5] Since there are limited long-term data on relapse, 5-FU is more often recommended and used by groups in the United Kingdom.[5] The European guidelines describe 3 formulations of imiquimod: 2.5% (not available in Canada), 3.75%, and 5%. The 2.5% and 3.75% imiquimod are recommended for once-daily use over two 2-week periods, with a 2-week rest in between. The 5% application is for 2 to 3 days per week over 4 to 16 weeks.[8]

A randomised trial comparing imiquimod 2.5% and 3.75% in 479 patients found them to be more effective than placebo, with complete and partial clearance rates to be 5.5% and 12.8% for placebo, 25.0% and 42.7% for imiquimod 2.5%, and 34.0% and 53.7% for imiquimod 3.75%, respectively ($P < .001$ each imiquimod vs placebo).[26] In 5 clinical trials, similar results were found for 5% imiquimod. Complete clearance rates ranged from 26.8% to 57.1% and partial clearance ranged from 36.6% to 72.1% for treatment regimens that lasted from 3 to 16 weeks ($P < .001$).[27-31] In 1 week, applying more than 3 times is not well tolerated.[32]

*Ingenol mebutate.* Canadian, UK, and European guidelines recommend the use of 0.015% ingenol mebutate for the face or scalp, with once-daily application over 3 days and 0.05% for the trunk/extremities once daily over 2 days.[1,5,8]

In 3 studies, partial clearance ranged from 49.1% to 75.4% and complete clearance was around 42.2% to 71% over a 2- to 3-day treatment period ($P < .0001$).[33-35] The short treatment period is beneficial for patients who have difficulty adhering to the longer regimens in other treatments such as imiquimod and 5-FU. As well, no drug interactions have been reported thus far with ingenol mebutate.[3] This treatment has also been used after cryosurgery with higher clearance rates, making it a recommended option for single and multiple AKs.[3]

*Other topicals.* Diclofenac, salicylic acid, and emollients were discussed in the guidelines as other topical treatments for AKs. UK and European guidelines discuss the use of 3% diclofenac in a 2.5% hyaluronic gel, with twice-daily application over 60 to 90 days for treating mild AKs.[5,8] One randomised trial found that 47% of actively treated patients were rated as completely improved by the investigator compared with the placebo group. Since diclofenac is a nonsteroidal anti-inflammatory drug (NSAID), its nondestructive properties can be favourable for early treatment before resorting to more invasive methods.[36] Currently, this formulation of diclofenac is not available in Canada.

The UK guidelines also recommend the use of emollients for mild AKs, although no trials on its use have been conducted.[5] This was not an option discussed by the other guidelines possibly due to its use as a placebo and lack of effect on the known pathophysiologic processes present in AKs.[5]

Finally, salicylic acid as a preliminary treatment to 5-FU has been recommended by both UK and European guidelines to remove overlying keratin. UK guidelines and European guidelines suggest using 10% salicylic acid with 0.5% 5-FU once daily for 6 to 12 weeks.[5,8] The evidence for this formulation of salicylic acid is limited. In a small randomised study (n = 66), using 0.5% 5-FU in 10% salicylic acid achieved a higher histologic clearance, lower clinical lesion counts, and lower recurrence rates than 2 cryotherapy treatments 3 weeks apart; however, drug-related adverse events were rated more severe than in the latter group.[37]

## Other Cases

*Single AKs.* All 3 guidelines recommend the use of cryosurgery for the removal of single AKs as first-line therapy.[1,5,8] Alternatively, Canadian guidelines suggest use of curettage or shave excision if the lesion is hyperkeratotic or requires histologic examination.[1,3] In the UK and European guidelines, curettage is rarely used and weakly recommended. Among topical options, 5-FU is considered a good treatment according to UK guidelines, but Canadian and European guidelines found weak to moderate evidence and do not recommend its use as strongly.[1,8] The guidelines for imiquimod also differ; Canadian guidelines highly recommend imiquimod, but it is not licensed in the United Kingdom and weakly recommended in Europe. This might be due to its cost and availability of other more accessible treatments, such as cryotherapy.[5] Combined therapies of 5-FU and 10% salicylic acid were only discussed in the European guidelines, but it is weakly recommended at this time.[8] This new combination therapy was not considered in the Canadian guidelines because it only became available after the literature search was completed.

*Thin AKs.* Only UK guidelines discuss treatment for thin AKs, using 5-FU as first line, followed by cryosurgery, topical diclofenac, imiquimod, or PDT. Curettage is rarely used as these lesions are superficial. Since thin AKs may not always require treatment, this might explain the paucity of studies on its management.

*Hypertrophic AKs.* All guidelines discuss the use of curettage as a first-line treatment for hypertrophic AKs. Curettage can be used alone or in conjunction with shave excision, electrodessication, or cryosurgery to achieve better clearance.[1,5,8] Although topical 5-FU, topical diclofenac, imiquimod, and PDT are rarely used for hypertrophic AK, 1 study of 66 patients comparing 0.5% 5-FU + 10% salicylic acid and cryosurgery found greater histological clearance (62%) with the 5-FU treatment than cryosurgery (42%).[37] This may be due to the inability of cryotherapy to treat perilesional skin, unlike field-directed topical therapies,[37] but these field therapies will need further investigations to assess their usability.

*Multiple AKs.* When treating multiple AKs, some differences appear in the 3 guidelines. Canadian guidelines strongly recommend imiquimod, ingenol mebutate, and PDT but report

low evidence for using 5-FU, laser resurfacing, and medium-depth chemical peel.[1] This is in contrast to UK and European guidelines, which strongly recommend 5-FU.[5,8] This divergence may be attributed to differing formulations being compared—in Europe, the 0.5% formulation is strongly preferred over the 5% formulation (weak recommendation), but only the latter is available and studied in Canada.[1,8]

In terms of alternative treatments, the UK guidelines list cryosurgery, diclofenac, imiquimod, and PDT as fair treatments.[5] The European guidelines differ slightly to strongly recommend 3.75% imiquimod and PDT, as well as providing weak support for cryosurgery and diclofenac.[8] These variations might reflect the differences in study method; the UK guidelines measured strength of recommendation based on amount of evidence obtained in the literature, while the European recommendations were graded as strong based on expert consensus.[5,8]

*Organ transplant patients.* The use of continuous systemic immunosuppression in organ transplant patients results in elevated risk of cutaneous malignancy. AK presentation in this patient population may have an atypical morphology and increased preposition to progress into SCC.[1] Based on Canadian guidelines, PDT was the most appealing option compared with other recommendations as evidence for other topicals and biopsy treatments are lacking.[1] European guidelines also recommended PDT, along with other treatments such as 5-FU, imiquimod, and cryotherapy or curettage in discrete or hyperkeratotic cases, respectively. However, these are only weak recommendations, as available data for this patient population are limited.[8]

UK guidelines only discuss the use of topical retonoids, systemic retinoids, or systemic cytotoxic agents in organ transplant recipients as a preventative measure due to the increased risk of progression from AK to SCC.[5] Systemic acitretin is considered a teratogen that may persist in the body for up to 3 years, and thus women should receive counselling regarding the need for long-term contraception.[1] Although there is little literature on the use of systemic chemotherapy agents, 1 study on capecitabine given to 15 transplant patients showed a 45% reduction of AKs compared with pretreatment levels.[38]

*Prevention.* The cornerstone in managing AKs is counselling patients on the need to reduce exposure to ultraviolet radiation. Primary prevention can be achieved through regular use of broad-spectrum sunscreen, sun-protective clothing, wide-brimmed hats, sunglasses, and avoiding exposure during peak hours.[3,8] Although prevention has been shown to reduce AKs and SCC, it alone is not sufficient in the management of AKs.[39]

Canadian guidelines concur with prevention as an adjunct to treatment. Particularly for immunosuppressed patients or those with a history of nonmelanoma skin cancers, treatment is essential.[1] In contrast, UK guidelines have strong recommendations for no therapy as an option for mild AKs or sunscreen applied twice daily for 7 months to protect against AK development.[5] European guidelines also recommend regular sunscreen application on a daily basis, but photoprotection is considered only a part of overall management.[8]

A new preventative therapy not discussed by any guidelines is the use of water-soluble B-vitamin nicotinamide (also called vitamin B3), which is thought to reduce UV radiation damage by enhancing DNA repair.[40] A recent large and well-designed RCT in Australia (n = 386) examined the effectiveness of nicotinamide 500 mg by mouth twice daily compared with placebo at preventing basal cell carcinoma and squamous cell carcinoma.[40] As a secondary end point, AK counts were considered. Compared with placebo, there were 13% ($P = .0001$) fewer AKs in the nicotinamide group at 12 months of follow-up.[40] Effects of the nicotinamide on AK counts were noticeable within 3 months of treatment initiation and sustained through the yearlong follow-up. There were no significant differences in adverse effects. This suggests nicotinamide may have a modest benefit in reducing new AKs and may serve as an adjunct to photoprotection use in high-risk patients.

## Conclusion

Although there is no single algorithm for the treatment of AKs, several guidelines exist to manage varying presentations of AKs. Patients are encouraged to avoid sun exposure through photoprotection, in conjunction with a specific treatment depending on the clinical presentation of the AK. Cryotherapy has the strongest recommendation for treatment of isolated AKs, although 5-FU, imiquimod, ingenol mebutate, and diclofenac can also be used. Shave excision can be used if the lesion is suspicious and requires histologic examination. For patients with multiple AKs, field therapies such as 5-FU, imiquimod, and ingenol mebutate are recommended, along with PDT as a destructive option. In cases where AKs are hyperkeratotic, the use of combination treatments of curettage or cryotherapy with a field therapy can be considered. In organ transplant recipients, field therapies are preferred for dispersed lesions and cryotherapy or curettage for individual lesions.

Our review summarises the current Canadian, European, and British guidelines and provides classification of their quality through an evidence rating scale. Clinicians should take into consideration the recommendations outlined, as well as costs, patient preference, cosmetic outcomes, comorbidities, and availability during the management of actinic keratoses.

### Declaration of Conflicting Interests

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## References

1. Poulin Y, Lynde CW, Barber K, et al. Non-melanoma skin cancer in Canada chapter 3: management of actinic keratoses. *J Cutan Med Surg*. 2015;19(3):227-238.
2. Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. *J Drugs Dermatol*. 2012;11(12): 1462-1467.
3. Costa C, Scalvenzi M, Ayala F, Fabbrocini G, Monfrecola G. How to treat actinic keratosis? An update. *J Dermatol Case Rep*. 2015;9(2):29-35.
4. Chetty P, Choi F, Mitchell T. Primary care review of actinic keratosis and its therapeutic options: a global perspective. *Dermatol Ther (Heidelb)*. 2015;5(1):19-35.
5. De Berker D, McGregor JM, Mohd Mustapa MF, Exton LS, Hughes BR. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol*. 2017;176(1):20-43.
6. Schmitt AR, Bordeaux JS. Solar keratoses: photodynamic therapy, cryotherapy, 5-fluorouracil, imiquimod, diclofenac, or what? Facts and controversies. *Clin Dermatol*. 2013; 31(6):712-717.
7. Kirby JS, Scharnitz T, Seiverling E V, Ahrns H, Ferguson S. Actinic keratosis clinical practice guidelines: an appraisal of quality. *Dermatol Res Pract*. 2015;2015:456071.
8. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) guidelines for the treatment of actinic keratosis—International League of Dermatological Societies in cooperation with the European Dermatology Forum–Short version. *J Eur Acad Dermatology Venereol*. 2015;29(11): 2069-2079.
9. Chiarello SE. Cryopeeling (extensive cryosurgery) for treatment of actinic keratoses: an update and comparison. *Dermatol Surg*. 2000;26(8):728-732.
10. Vatve M, Ortonne JP, Birch-Machin MA, Gupta G. Management of field change in actinic keratosis. *Br J Dermatol*. 2007;157(suppl 2):21-24.
11. Deonizio JMD, Mulinari-Brenner FA. Cryopeeling for treatment of photodamage and actinic keratosis: liquid nitrogen versus portable system. *An Bras Dermatol*. 2011;86(3):440-444.
12. Ceilley RI, Jorizzo JL. Current issues in the management of actinic keratosis. *J Am Acad Dermatol*. 2013;68(1)(suppl 1):S28-S38.
13. Pariser D, Loss R, Jarratt M, et al. Topical methyl-aminolevulinate photodynamic therapy using red light-emitting diode light for treatment of multiple actinic keratoses: a randomized, double-blind, placebo-controlled study. *J Am Acad Dermatol*. 2008;59(4):569-576.
14. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp. *Arch Dermatol*. 2004;140:41.
15. Szeimies RM, Matheson RT, Davis SA, et al. Topical methyl aminolevulinate photodynamic therapy using red light-emitting diode light for multiple actinic keratoses: a randomized study. *Dermatol Surg*. 2009;35(4):586-592.
16. Dirschka T, Radny P, Dominicus R, et al. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinatecreamandplacebo.*BrJDermatol*.2012;166(1): 137-146.
17. Pariser DM, Lowe NJ, Stewart DM, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol*. 2003;48(2)(suppl):227-232.
18. Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol*. 2007;157(1):87-91.
19. Braathen LR, Szeimies RM, Basset-Seguin N, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. International Society for Photodynamic Therapy in Dermatology, 2005. *J Am Acad Dermatol* 2007;56(1):125-143.
20. Scola N, Terras S, Georgas D, et al. A randomized, half-side comparative study of aminolaevulinate photodynamic therapy vs. CO2 laser ablation in immunocompetent patients with multiple actinic keratoses. *Br J Dermatol*. 2012;167(6):1366-1373.
21. Togsverd-Bo K, Haak CS, Thaysen-Petersen D, et al. Intensified photodynamic therapy of actinic keratoses with fractional CO2 laser: a randomized clinical trial. *Br J Dermatol*. 2012;166(6):1262-1269.
22. Witheiler DD, Lawrence N, Cox SE, Cruz C, Cockerell CJ, Freemen RG. Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Dermatol Surg*. 1997;23(3):191-196.
23. Coleman WP, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg*. 1996;22(1):17-21.
24. Askew DA, Mickan SM, Soyer HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis: a systematic review of randomized controlled trials. *Int J Dermatol*. 2009;48(5):453-463.
25. Gupta AK, Davey V, McPhail H, Hart DA. Evaluation of the effectiveness of imiquimod and 5-fluorouracil for the treatment of actinic keratosis: critical review and meta-analysis of efficacy studies. *J Cutan Med Surg*. 2005;9(5):209-214.
26. Hanke CW, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. *J Am Acad Dermatol*. 2010;62(4):573-581.
27. Szeimies RM, Gerritsen MJP, Gupta G, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol*. 2004;51(4): 547-555.
28. Lebwohl M, Swanson N, Anderson LL, Melgaard A, Xu Z, Berman B. Supplement to: Ingenol mebutate gel for actinic keratosis. *N Engl J Med*. 2012;366(11):1010-1019.
29. Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or

two courses of treatment of actinic keratoses on the head. *Br J Dermatol*. 2007;157(1):133-141.
30. Jorizzo J, Dinehart S, Matheson R, et al. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. *J Am Acad Dermatol*. 2007;57(2):265-268.
31. Korman N, Moy R, Ling M, et al. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis. *Arch Dermatol*. 2005;141(4):467-473.
32. Gebauer K, Shumack S, Cowen PSJ. Effect of dosing frequency on the safety and efficacy of imiquimod 5% cream for treatment of actinic keratosis on the forearms and hands: a phase II, randomized placebo-controlled trial. *Br J Dermatol*. 2009;161(4):897-903.
33. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol*. 2004;50(5):714-721.
34. Siller G, Gebauer K, Welburn P, Katsamas J, Ogbourne SM. PEP005 (ingenol mebutate) gel, a novel agent for the treatment of actinic keratosis: results of a randomized, double-blind, vehicle-controlled, multicentre, phase IIa study. *Australas J Dermatol*. 2009;50(1):16-22.
35. Anderson L, Schmieder GJ, Werschler WP, et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol*. 2009;60(6):934-943.
36. Wolf JEJ, Taylor JR, Tschen E, Kang S. Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol*. 2001;40(11):709-713.
37. Simon JC, Dominicus R, Karl L, Rodríguez R, Willers C, Dirschka T. A prospective randomized exploratory study comparing the efficacy of once-daily topical 0.5% 5-fluorouracil in combination with 10.0% salicylic acid (5-FU/SA) vs. cryosurgery for the treatment of hyperkeratotic actinic keratosis. *J Eur Acad Dermatology Venereol*. 2015;29(5):881-889.
38. Jirakulaporn T, Endrizzi B, Lindgren B, Mathew J, Lee PK, Dudek AZ. Capecitabine for skin cancer prevention in solid organ transplant recipients. *Clin Transplant*. 2011;25(4):541-548.
39. Chetty P, Choi F, Mitchell T. Primary care review of actinic keratosis and its therapeutic options: a global perspective. *Dermatol Ther (Heidelb)*. 2015;5(1):19-35.
40. Chen AC, Martin AJ, Choy B, et al. A phase 3 randomized trial of nicotinamide for skin-cancer chemoprevention. *N Engl J Med*. 2015;373(17):1618-1626.

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