

Non-melanoma Skin Cancer in Canada

Chapter 3: Management of Actinic Keratoses

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Abstract

Background: Actinic keratosis (AK) and cheilitis (AC) are lesions that develop on photodamaged skin and may progress to form invasive squamous cell carcinomas (SCCs).

Objective: To provide guidance to Canadian health care practitioners regarding management of AKs and ACs.

Methods: Literature searches and development of graded recommendations were carried out as discussed in the accompanying introduction (chapter 1 of the NMSC guidelines).

Results: Treatment of AKs allows for secondary prevention of skin cancer in sun-damaged skin. Because it is impossible to predict whether a given AK will regress, persist, or progress, AKs should ideally be treated. This chapter discusses options for the management of AKs and ACs.

Conclusions: Treatment options include surgical removal, topical treatment, and photodynamic therapy. Combined modalities may be used in case of inadequate response. AKs are particularly common following the long-term immunosuppression in organ transplant patients, who should be monitored frequently to identify emerging lesions that require surgery.

Résumé

Contexte : Les kératoses actiniques (KA) et les chéilites actiniques (CA) sont des lésions qui se développent sur la peau photoendommagée et qui peuvent progresser vers le carcinome spinocellulaire (CSC) invasif.

Objectif : Fournir des conseils aux professionnels canadiens de la santé au sujet de la gestion des KA et des CA.

Méthode : Nous avons procédé à une étude documentaire et à l'élaboration de catégories de recommandations, comme on peut le lire dans l'introduction qui accompagne le présent résumé (Chapitre 1 des Lignes directrices sur le cancer de la peau non mélanique).

Résultats : Le traitement des KA permet une prévention secondaire du cancer de la peau photoendommagée. Comme il est impossible de prévoir si une KA donnée régressera, persistera ou progressera, les KA devraient idéalement être traitées. Ce chapitre présente les options de prise en charge des KA et des CA.

Conclusions : Les options de traitement comprennent l'excision chirurgicale, le traitement topique ou la thérapie photodynamique. Des méthodes combinées peuvent être utilisées en cas de réponse inadéquate. Les KA sont particulièrement courantes après une immunosuppression prolongée chez les patients greffés qui devraient être examinés fréquemment pour dépister les nouvelles lésions nécessitant une chirurgie.

Keywords

actinic keratosis, actinic cheilitis, photodynamic therapy, cryosurgery, imiquimod, fluorouracil, ingenol mebutate

Actinic keratoses (AKs) are cutaneous lesions typically arising on areas of chronic exposure to ultraviolet light. These lesions, sometimes called keratinocyte intraepidermal neoplasias,¹ are by definition confined to the epidermal layer of the skin. Because AKs are typically small (3–6 mm), flat, pink or nonpigmented, and painless, they are sometimes detected by palpation, as a result of their

sandpaper-like texture, rather than by visual inspection or patient report.²

AKs can be difficult to distinguish clinically from squamous cell carcinoma (SCC)³ and other forms of non-melanoma skin cancer (NMSC), although dermatoscopy may help establish the nature of the lesion.^{4,5} Other diagnoses to consider include seborrheic keratosis, discoid lupus, stucco

keratosis, solar lentigo, porokeratosis, and viral warts.⁶ Furthermore, AKs vary in form and presentation. Thickened/hyperkeratotic and pigmented AKs occur, and diameters can range to >1 cm; patients occasionally report pain.⁷

Authorities debate whether AKs should be regarded as SCC in situ or as premalignant precursors to invasive SCC.⁸ However, it is clear that they represent an intermediate stage in a multistep evolution of SCC (see chapter 4).⁹ Treatment of AKs offers a chance at secondary prevention of skin cancer in sun-damaged skin. Because it is impossible to predict whether a given AK will regress, persist, or progress, AKs should ideally be treated,¹⁰ and treatment is essential in individuals who are immunosuppressed and in those with a history of NMSC. Individuals with a history of AKs should be monitored periodically for the appearance of SCC or other new lesions.

Occurrence and Natural History

AKs are common in older, fair-skinned individuals. In general, AK incidence rises with patient age, higher altitude, and proximity to the equator.⁶

In the United States, AKs account for an estimated 11.5% of all dermatologist visits.¹¹ In Australia, which is thought to have the highest prevalence in the world, 40% to 50% of individuals older than 40 years have had AKs.⁶ AK rates reported for northwest England (15% in men older than 40 years; 6% in women) may be more reflective of the Canadian population.¹² However, AK prevalence and incidence in Canada have not been studied.

AKs often present in clusters on sun-exposed areas of the arms, head, and neck.^{13,14} The sun-damaged skin where lesions occur is a dynamic environment in which AKs continuously develop and regress and, at a low rate, progress to form frank SCCs. The rate of spontaneous regression has been reported to be as low as 15 per 100 AKs per year¹⁵ or as great as 74 per 100.¹⁶ One careful photographic follow-up study reported that approximately 0.6% of lesions progressed

to in situ or invasive SCC over 1 year, whereas 55% of AKs spontaneously regressed clinically.¹⁷ However, unless the area has been surgically excised, AKs that appear by clinical criteria to have regressed may recur after ≥ 4 months.^{16,18}

The relationship between AKs and SCCs is evident from their shared histologic features, location, and natural history. At least half of SCCs are found in proximity to AKs¹⁹ or underlying lesions initially diagnosed as AKs.⁸ While up to 80% of SCCs have been documented to begin as AKs, the rate of progression depends on the grade and features of the AK.⁸ Lesions that are hyperkeratotic, painful, or atypically broad are thought to progress at a higher rate than that of typical AKs.²⁰ They may also prove more difficult to clear with standard therapies.^{7,21,22}

These findings support the concept of field cancerization (see chapter 1)—namely, that subclinical AKs, AKs, and in situ and invasive SCCs all emerge from a field of photodamaged epidermis where the keratinocytes carry ultraviolet-induced mutations, predisposing them to abnormal growth. Field cancerization has important implications for treatment, as discussed below.¹⁰

Overview of the Clinical Literature on AKs

The highest-quality evidence on treatment efficacy comes from carefully conducted randomized controlled trials. Such reports, involving active comparators²³⁻²⁶ and/or a placebo group,²⁷⁻³¹ exist in the AK literature, although patient populations may be small and blinding is often questionable. AK research is singularly well suited to intraindividual comparison studies—for example, split-face or split-scalp studies, in which different therapies are used to treat otherwise-identical areas of photodamaged skin.^{22,26,32-34}

Efficacy outcomes differ across studies in the AK literature, making comparisons difficult. In particular, some studies report the proportion of lesions that respond to treatment,

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whereas others report the rate of complete clearance within the treatment field. Regulatory agencies generally focus on complete clearance. However, less ambitious end points—such as reduction in the size, grade, or number of a patient's AKs—are also reported in the literature.

The size of the treated field, the number of AKs at baseline, and the time frame for evaluating treatment also vary from study to study. For some treatments, limited long-term data are available. However, the most common outcome—and the one that is most readily compared across studies—is response evaluated at the time that the skin has healed after therapy, typically 2 to 12 weeks afterwards. Here, we use short-term clearance as the primary outcome for judging treatment efficacy. More ambitious and less ambitious clinical outcomes (eg, persistent clearance after >1 year and 75% reduction in lesion count, respectively) are also reported in the literature and were considered in developing this chapter.

Studies also vary with respect to the AKs included. AKs from different areas of the skin (eg, scalp vs extremities) differ with respect to AK form and prognosis, as well as with respect to tolerance to treatment; this distinction is not always made when reporting outcomes. Furthermore, patients with large, high-grade, thickened, or hyperkeratotic AKs are excluded from most clinical trials,^{31,35,36} although they may be included in studies on photodynamic therapy (PDT), in which curettage of hypertrophic AKs is allowed.³⁷⁻³⁹ For these reasons, it may not be possible to generalize findings across reports.

AK occurring on the lips (actinic cheilitis [AC]) is a clinically and cosmetically important subtype with a dearth of high-quality studies. The available information on AC treatment outcomes is discussed in a subsection below.

Finally, the patient population differs across AK studies. Immunocompromised individuals represent a special population at high risk of developing AKs, SCC, and metastatic SCC. Studies in transplant patients are treated separately at the end of this chapter. With extremely high frequency of SCCs in this population, it is feasible to analyze tumour development, to determine if field therapy to clear AKs can also reduce incidence of SCCs—a hypothesis that has been difficult to test in the immunocompetent population.² As discussed below, some data indicate that repeated rounds of PDT can indeed prevent SCCs in this high-risk population.

Treatment Options for AKs

Surgical Removal

AKs are not routinely surgically excised, and a biopsy is generally unnecessary for isolated AKs of typical size and presentation. However, a biopsy may be required for recurrent lesions and for new lesions that require histologic diagnosis to rule out the possibility of invasive SCC.

Shave excision is commonly used for removal of hypertrophic AKs. Histology of the surrounding epidermis may

provide evidence of field abnormalities or reassurance that the biopsied lesion has been definitively removed. Curettage may be used alone or in conjunction with shave excision, electrodesiccation, or cryosurgery. Regardless, the patient should be monitored regularly for the emergence of additional AKs in the photodamaged field, and the need for ongoing photoprotection should be reinforced.

Solitary lesions may also benefit from surgical excision. The disadvantages of surgical procedures are that only a limited number of visible lesions may be treated, anesthesia is required, and patients may experience permanent depigmentation and scarring.

Cryosurgery

Local treatment with liquid nitrogen (LN₂; cryosurgery) is the most common approach to AK management. Cryosurgery is inexpensive, accessible, and well tolerated. Cryosurgery outcomes are operator dependent and vary depending on freeze time,⁴⁰ the number of LN₂ applications, and other parameters. Reported AK clearance rates vary substantially across studies, due in large part to the lack of standardization of this procedure.

One prospective study on facial and scalp AKs showed that short-term complete clearance of lesions occurred in 57% of patients.⁴⁰ In another study using LN₂ cryosurgery, 68% of patients were free of AKs 6 weeks after receiving 1 or 2 treatment sessions.²³ However, further lesions can be expected to develop, as cryosurgery targets only clinically evident lesions. Indeed, at 1 year after cryosurgery, only 4% of patients remained free of AKs in the treated area; in the same study, topical 5% 5-fluorouracil (5FU) or 5% imiquimod commonly led to sustained clearance over this period. Thus, as expected, cryosurgery treatment was not effective as field therapy.²³

Lesions typically heal with little discomfort, but cosmesis is sometimes unsatisfactory: longer freeze times or multiple applications of LN₂ can improve clearance rates, but they also increase the risk of local scarring and hypo- or hyperpigmentation.⁴⁰

5% 5FU Cream

5% 5FU was first used as a treatment for discrete AKs.^{23,25,27,41,42} It may also be used as field therapy, although evidence supporting this approach is limited.^{23,27,43} 5% 5FU cream is applied twice daily for up to 4 weeks. This regimen leads to local inflammation, erosion, and pain, which may be poorly tolerated and may limit the duration of treatment.⁴¹ Short-term cosmetic outcomes are good.²⁷

Overall, about half of patients in studies of 5% 5FU achieve complete clearance of AKs, whereas >90% experience some reduction in lesion number.²⁷ In one study, 43% of patients achieved complete clearance of facial AKs within 4 weeks of completing treatment.⁴¹ Another study found

slightly better short-term outcomes (67% achieving clearance of AKs at 4 weeks) but substantial recurrence of AKs in the treated field (33% with sustained clearance after 1 year).²³

A lower-strength formulation of 5FU has been studied but is not marketed in Canada.⁴⁴ In addition, alternative dosing regimens with 5% 5FU have been proposed, which may improve tolerability at the cost of extending treatment duration.⁴⁵

5% Imiquimod Cream

Imiquimod has been evaluated in clinical trials in which the cream was applied to affected areas rather than to isolated AKs; it continues to be used primarily as a field therapy. While twice-weekly application for up to 16 weeks is consistent with Canadian packaging,³⁰ most of the clinical literature from Europe and elsewhere documents the effects of 5% imiquimod dosed 3 times weekly. Three-times-weekly dosing, applied in 4-week treatment cycles, is common in Canadian practice, reflecting the weight of the clinical evidence.

Still more frequent dosing of 5% imiquimod has been tested but is not well tolerated.⁴⁶ A meta-analysis combining twice- and 3-times-weekly dosing suggests that short-term clearance occurs in approximately half of patients with facial and scalp AKs.⁴⁷

Imiquimod treatment at various doses leads to a transient increase in the number of visible AKs in the treated field.^{48,49} Treatment-emergent AKs are thought to arise from subclinical lesions. They can be seen after the second week in each treatment cycle and should be regarded as evidence of efficacy. These lesions regress with continued application of imiquimod.^{30,49,50}

With 5% imiquimod administered 3 times weekly for 1 or 2 four-week cycles, 73% of patients maintained clearance in the treated field for at least 1 year. This rate was significantly greater than that in patients using 5% 5FU (33%) or receiving 2 sessions of cryosurgery (4%).²³ Cosmetic results were judged excellent in most cases.²³

3.75% Imiquimod Cream

In a standard course, 3.75% imiquimod is used as a field therapy. It is applied daily to the face or scalp for two 2-week cycles, separated by a 2-week rest period. Local reactions with imiquimod include erythema (with minimal pain⁵¹) as well as scabbing or crusting. These local responses occur not only in clinically evident AKs but elsewhere in the treatment field, where AKs were not clinically evident at baseline. Trials of 3.75% imiquimod reported fewer withdrawals due to adverse events, compared to 5% imiquimod²; differences between the 2 formulations with regard to tolerability or efficacy have not been directly tested.

Eight weeks after treatment, complete clearance occurred in approximately 36% of patients.⁵² However, within 1 year, further AKs developed in half of these patients.⁵³ Longer initial treatment, consisting of two 3-week cycles, did not

improve the initial clearance rate⁴⁸ but increased the rate of sustained clearance.^{52,53}

Ingenol Mebutate Gel

Topical ingenol mebutate is available at 2 concentrations—one (0.015%) for the face and scalp and the other (0.05%) for the trunk and extremities. For facial and scalp areas, dosing is once daily for 3 days, a shorter period than for the other available topical agents, which is potentially advantageous with respect to treatment adherence.⁵⁴ For the trunk and extremities, the 0.05% concentration is to be applied on 2 consecutive days.^{31,55}

Ingenol mebutate has been studied in a set of 4 multicentre double-blind randomized controlled trials: 2 for discrete AKs of the face and scalp (n = 547) and 2 for discrete AKs of the trunk or extremities (n = 458). Outcomes were followed up to 2 months after treatment. In the facial and scalp studies, full clearance occurred in 4% of placebo-treated patients and in 42% of patients receiving ingenol mebutate 0.015% ($P < .001$); median reductions in lesion count in the 2 groups were 0% and 83%, respectively. In the truncal and acral AK studies, full clearance occurred in 5% of placebo-treated patients and in 34% of patients receiving ingenol mebutate 0.05% ($P < .001$); median reductions in lesion count in the 2 groups were 0% and 75%, respectively.³¹

Ingenol mebutate treatment induced local reactions (erythema, flaking, erosions, and crusting), which resolved by 15 to 29 days posttreatment. Scarring and pigment changes were judged absent or minimal.³¹

In a follow-up study of patients achieving clearance with ingenol mebutate (N = 184), approximately half remained clear after 12 months, and overall lesion count was reduced >85% in the treated area, relative to baseline. Eleven percent of facial/scalp AK patients and 22% of truncal/acral AK patients underwent cryosurgery or some other treatment for AKs during the study period.⁵⁶

PDT and Daylight PDT

Two PDT systems are available for AK treatment—one using blue light and the photosensitizer 5-aminolevulinic acid (ALA; Levulan® Kerastick®), the other using red light and methyl aminolevulinate (MAL; Metvix®). In conventional PDT, with red or blue light, procedures are carried out in the dermatologist's office. Laser illumination in place of other light sources in PDT (laser-activated PDT) may also be advantageous.^{57,58}

After local reactions have healed (mostly erythema and crusting), cosmesis is generally excellent.^{59,60} PDT systems offer reasonable options for AKs disseminated over large areas. In more advanced AKs, curettage is generally required before PDT to remove hyperkeratotic tissue. Despite this pretreatment, thicker AKs respond at a reduced rate and may require more treatment sessions to achieve clearance.^{22,61,39}

PDT does not effect a full reversal of photodamage in all instances; AKs may begin to emerge after 4 to 6 months.^{18,62} In patients with a history of NMSC, 2 sessions of ALA-PDT delayed the emergence of AKs and other lesions from severely photodamaged skin, relative to placebo treatment. The suppression of new lesions was statistically significant over the first 12 months but was lost after 27 months.⁶³

PDT causes a burning sensation while the treated area is being illuminated and, to a lesser extent, following treatment.⁶⁴ Various strategies have been proposed to block⁶⁵ or minimize pain in PDT, including changing the source, intensity,⁶⁶ or spectrum of the light⁶⁷ or the timing of illumination.^{39,68} Patients who have experienced both ALA-PDT and MAL-PDT consistently report that the latter is preferable with respect to pain during and after light treatment.⁶⁹

Recently, a variant of PDT has been explored in which MAL cream is applied to the photodamaged skin and patients sit in bright sunlight for 2 hours, wearing sunscreen as usual for ultraviolet protection. Pain is reported to be significantly reduced under these conditions, relative to conventional MAL-PDT.^{70,71} One intraindividual comparison study on facial and scalp AKs showed that local reactions (crusting and erythema) and 3-month clearance rates were similar with conventional or daylight MAL-PDT. With either source of illumination, clearance rates were lower for hyperkeratotic versus thin lesions, but outcomes were similar for the 2 PDT protocols.³⁴

Efficacy does not appear to depend critically on light intensity, as long as a threshold is reached.⁷¹ Studies of daylight PDT have been carried out during the warmer months in northern temperate areas (Switzerland and Scandinavia); similar protocols are likely to be successful in parts of Canada sharing these same latitudes.

Other Therapies

Diverse approaches have been used to clear AKs, including medium-depth chemical peels^{43,72,73} and laser resurfacing.⁷⁴⁻⁷⁶ Supportive data are limited. Medium-depth chemical peeling is an operator-dependent technique, and patients should be referred to a specialist with experience in the procedure. In a direct comparison of laser resurfacing and 5% 5FU, the topical treatment led to some clearance of AKs but with substantial recurrence after 1 year. Conversely, a single session of laser resurfacing treatment provided effective field treatment of photodamaged skin, with 59% of subjects remaining free of recurrent AKs. However, this treatment led to hypopigmentation in many subjects.⁷⁷ An additional topical option, diclofenac, is not currently available in Canada.

Combined Treatment Modalities

Therapeutics with different mechanisms of action may be combined simultaneously or sequentially, potentially improving outcomes relative to either monotherapy. Many

such combinations have been explored, but most studies are preliminary.¹⁹ One option that appears feasible in routine practice is the combination of cryosurgery with topical treatment.

Because cryosurgery is purely lesion-directed, it is reasonable to follow up with an adjunctive field-directed therapy.^{35,78} One study found that a standard course of 3.75% imiquimod, initiated 1 to 2 weeks after cryosurgery, led to significantly greater clearance at 6 months, relative to cryosurgery plus placebo treatment.³⁵ A similar study explored the use of 5% imiquimod, applied after cryosurgery, to treat lesions that were not eliminated by cryosurgery alone.⁷⁸

In both studies, imiquimod exposed and subsequently cleared AKs in the treated area that were not clinically evident at baseline, delaying the emergence of new AKs. Imiquimod also increased the clearance of the cryotreated lesions themselves, but it is not clear from these studies if sequential treatment was significantly more effective than imiquimod alone.

Sequential use of cryosurgery and imiquimod,^{78,79} 5FU, or other topical agents appears to be widespread and is assumed to be beneficial relative to monotherapy.¹⁹ However, the optimal way to combine these 2 modalities is still not known.

Treatment Options for AC

An AK occurring on photodamaged lips, termed an actinic cheilitis (AC), presents as a white lesion with interspersed red areas. The vermilion border with the skin may be blurred.⁸⁰ ACs are found almost exclusively on the lower lip and are less common in women, apparently because of the ultraviolet protection conferred by lipstick.⁸¹

As with other AKs, palpation may be helpful in the diagnosis of ACs.⁸² Histologic analysis of the vermilion surrounding ACs commonly identifies foci of SCC.⁸³ Because SCCs in this area have an elevated rate of metastasis,⁸⁴ field-directed therapy may be preferred over localized cryosurgery for ACs.

Surgical vermilionectomy (resection of the entire epithelial layer) allows for long-term clearance of ACs, as well as full histologic evaluation of the photodamaged field,⁸³ but poses a risk of cosmetic damage or functional impairment.⁸¹ Less invasive field-directed approaches include topical treatment with 5% 5FU,⁸⁵ ALA-PDT,^{36,86,87} and MAL-PDT.^{88,89} Imiquimod has also been explored for AC; despite Canadian labelling that restricts use of 3.75% and 5% imiquimod on the lips, this approach is common in clinical practice.⁹⁰

If available, laser resurfacing of the lip and laser-activated PDT are other field-directed approaches with good short- and long-term clearance and good to excellent cosmesis.^{58,76,91,92} Electrodesiccation, which may be more widely accessible, offers similar short-term outcomes to those of laser resurfacing.⁹³

Table 1. Treatment Recommendations for Managing Actinic Keratosis.

Treatment Recommendation	Level of Evidence ^a	Strength of Recommendation ^b
1. AKs with atypical morphology or presentation or resistant to treatment should be biopsied/excised.	NA	Strong
2. Isolated AKs should generally be treated with cryosurgery or a surgical procedure, if appropriate, given location and patient parameters. Curettage or direct surgical excision are preferred options if the lesions are hyperkeratotic. Other therapeutic options include the following:	Moderate ⁴⁰	Strong
• 5% 5-fluorouracil	Moderate ^{23,27}	Weak
• 5% imiquimod	High ^{23,47,49,50}	Strong
• 3.75% imiquimod	High ^{48,52,53}	Strong
• Ingenol mebutate	High ^{31,55,107}	Strong
3. Areas with clustered AKs and those with histologic evidence of field cancerization should be treated with field-directed therapies. Therapeutic options include the following:		
• 5% 5-fluorouracil	Low ^{23,27}	Weak
• 5% imiquimod	High ^{23,47,49,50}	Strong
• 3.75% imiquimod	High ^{48,52,53}	Strong
• Ingenol mebutate	High ^{31,55,107}	Strong
• PDT ^c	High ^{18,34,38,57,64,69,71,108-110}	Strong
• Laser resurfacing if available	Low ⁷⁷	Weak
• Medium-depth chemical peel	Low ^{43,74}	Weak
4. If cryosurgery or surgery is used in patients with solar elastosis or other evidence of extensive photodamage, field-directed therapy may be applied once healing is complete. Options include the following:	Moderate ^{35,78}	Strong
• 5% or 3.75% imiquimod		
• 5% 5-fluorouracil		
• Ingenol mebutate		
• PDT		
5. Patients with evidence of photodamage or a history of AKs should be regularly monitored for new lesions, with an increase in monitoring frequency if any of the following apply:	NA	Strong
• History of NMSC		
• History of nonresponsive AKs		
• Ongoing systemic immunosuppression		
6. ACs may be treated with any of the following modalities:		
• Cryosurgery	All low ^{80,85,88}	Strong
• Field-directed topical agents, ^d including 5-fluorouracil and imiquimod	Low ^{36,86-89}	Weak
• PDT ^c	Low ⁸³	Weak
• Complete or partial vermilionectomy	Low ^{91,92}	Weak
• Laser resurfacing	Low ⁹³	Strong
• Electrodesiccation and curettage	NA	Strong
Lesions that do not respond to these measures should be biopsied to analyze for evidence of NMSC and treated accordingly.		
7. Organ transplant recipients and others with long-term systemic immunosuppression and clinical evidence of AKs may receive field-directed therapies to prevent the emergence of AKs and NMSC in areas of photodamage. Therapeutic options include the following:		
• Imiquimod	Low ⁹⁵	Strong
• Ingenol mebutate	NA	Weak
• PDT ^c	Moderate ^{100,102,104}	Strong

(continued)

Table 1. (continued)

Treatment Recommendation	Level of Evidence ^a	Strength of Recommendation ^b
Other modalities that have been used include the following: <ul style="list-style-type: none"> • Chemo-wrapping with 5-fluorouracil • Laser resurfacing • Medium-depth chemical peel 		
8. In organ transplant recipients, a high level of suspicion for malignant transformation should be noted. Lesions that do not respond to treatment should be biopsied/excised.	NA	Strong

Abbreviations: 5FU, 5-fluorouracil; AC, actinic cheilitis; AK, actinic keratosis; ALA-PDT, 5-aminolevulinic acid; MAL-PDT, methyl aminolevulinate; NMSC, non-melanoma skin cancer; PDT, photodynamic therapy.

^aLevel of evidence is evaluated as high, moderate, low, or very low, corresponding to the likelihood that the benefits of the therapeutic approach will stand up to further testing. Therapeutic approaches supported by meta-analyses or multiple randomized controlled trials that are free from significant bias have a high level of evidence. Studies based on intraindividual comparisons may also have a high level of evidence, particularly when both treatments are delivered by a health care professional. Options supported by methodologically weaker studies (non-randomized controlled trials) and those with weak effects or inconsistent data across studies have a low or very low level of evidence. Statements that are based on biological plausibility or other indirect arguments are listed as NA, indicating that direct support for the claim is not available. (See chapter 1 for general methods.)

^bStrength of recommendation is evaluated as strong or weak, depending on the confidence that the treatment is more helpful than the alternatives, including nontreatment. Hence, therapies with a high level of evidence regarding efficacy may receive a weak recommendation if the risk of adverse response is high or if this risk is not well known. Conversely, approaches with no likelihood of doing harm may receive a strong recommendation, even if they are supported by limited evidence. (See chapter 1 for general methods.)

^cFollowing curettage on any thickened AK lesions; includes ALA-PDT and MAL-PDT, illuminated with red or blue light, laser light, or daylight.

^dNote that use of imiquimod or ingenol mebutate on the mouth is contrary to Canadian labelling.

AKs in Organ Transplant Recipients

Because organ transplant recipients (OTRs) require continuous systemic immunosuppression, AKs are common; the rate of SCC development in this group exceeds that in immunocompetent people by ~100-fold.^{94,95} AKs in OTRs may be morphologically different from typical AKs, appearing more prominent (wartlike) and hyperkeratotic, and their SCCs are at elevated risk of local recurrence and metastasis.⁹⁴

While systemic acitretin is commonly prescribed to OTRs to restrict the development of AKs, this retinoid acts by promoting epidermal turnover. It does not remove transformed cells from the epidermis, so continuous treatment is needed to avoid rebound.^{94,96} Unfortunately, patients' acceptance of and persistence with acitretin are limited.⁹⁶ Furthermore, despite its clear effect on AK number, acitretin does not consistently slow the emergence of SCCs.^{97,98} Acitretin, a strong teratogen that may persist in the body for ≥2 years, should be avoided in treating women of childbearing potential unless strict contraceptive measures are followed.

Field treatment is essential to minimize the emergence of AKs and prevent the growth of invasive or metastatic SCCs on photodamaged skin. The best-studied approaches are topical treatment and PDT. In a direct comparison with MAL-PDT in OTRs, 5FU was less effective at resolving AKs and yielded poorer cosmesis.⁹⁹

Despite theoretical concerns that imiquimod, an immunomodulator, might be inappropriate for or ineffective in immunosuppressed patients, there is no evidence that it promotes graft rejection, and a full 16-week course of imiquimod 3 times weekly significantly reduced the number of

AKs in OTR patients.^{29,95} Over 8 months of observation, the number of SCCs was also significantly lower with imiquimod, relative to a vehicle control.⁹⁵

PDT is an attractive option for AK and NMSC prophylaxis in OTRs because of the ability to treat wide areas. AK clearance with ALA-PDT appears equally effective in immunosuppressed and immunocompetent people.¹⁰⁰ In one study of OTRs with a prior history of SCCs, ALA-PDT was administered on a cyclic basis with pretreatment curettage of hyperkeratotic AKs. Patients received up to 14 treatments over 2 years.¹⁰¹ This procedure led to a significant decrease in the incidence of new SCCs over 1 to 2 years, relative to the pretreatment period ($P < .001$). Although this was a small ($N = 12$) and uncontrolled study, it is notable that all patients experienced fewer SCCs, with a median 95% decrease (range, 87.5%-100%) in SCC incidence with cyclic PDT.¹⁰¹

MAL-PDT led to complete short-term clearance of treated lesions in >70% of OTRs.^{102,103} In addition, over the course of 1 year, a single session of MAL-PDT significantly delayed the appearance of new lesions relative to placebo treatment.¹⁰⁴ Over the longer term (≥2 years), MAL-PDT did not appear to reduce the incidence of AKs¹⁰⁵ or SCCs.¹⁰⁶ However, this discrepancy, relative to longer-term outcomes with ALA-PDT,¹⁰¹ may be explained in part by less frequent follow-up sessions in the MAL-PDT studies. The optimal timing of retreatment to extend the benefits of PDT remains uncertain.

Irrespective of the field treatment chosen, OTRs should be monitored frequently to identify emerging lesions requiring surgery.⁹⁴

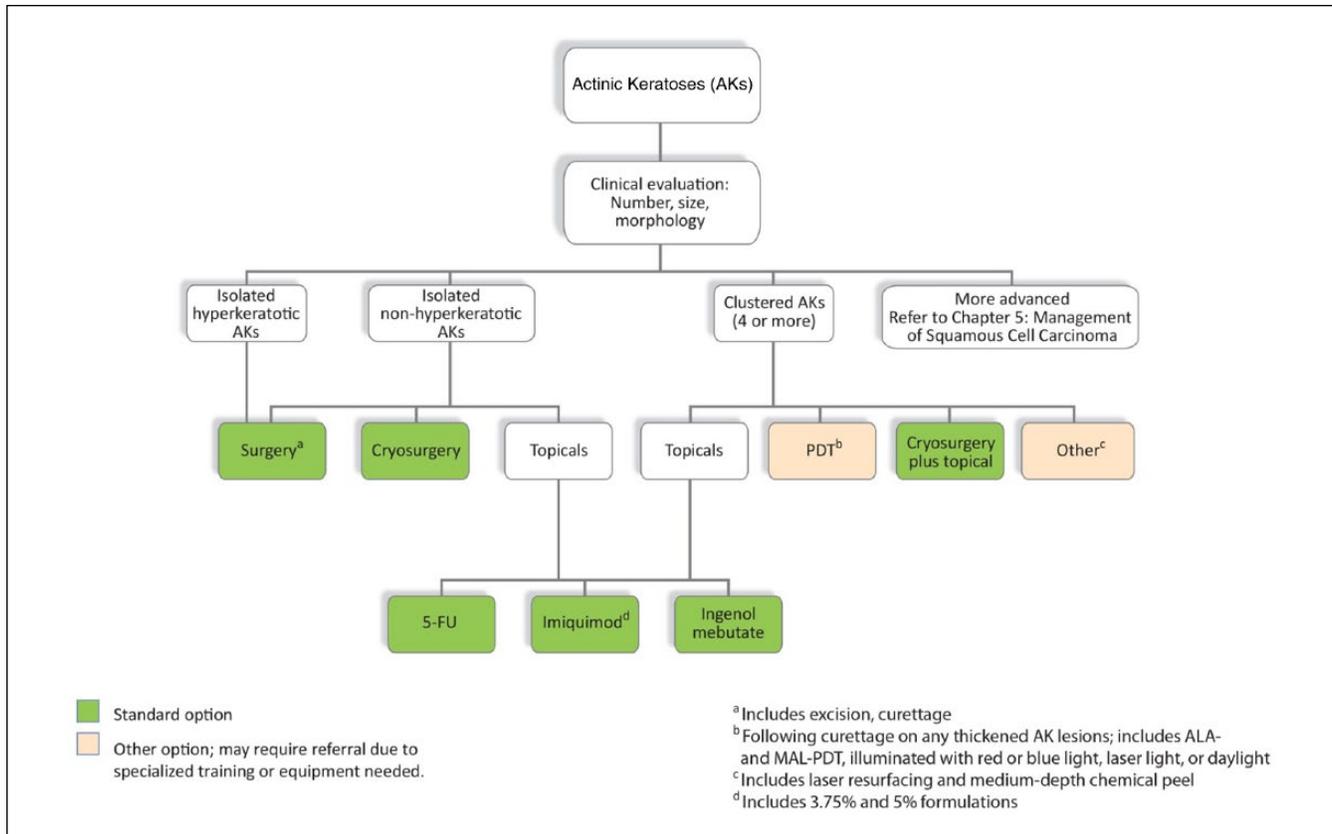


Figure 1. Management of actinic keratosis.

5FU, 5-fluorouracil; AK, actinic keratosis; ALA, 5-aminolevulinic acid; MAL, methyl aminolevulinic acid; PDT, photodynamic therapy.

Methods

Literature searches and development of graded recommendations were carried out as discussed in the accompanying introduction (chapter 1 of the Canadian NMSC guidelines).

Conclusions

The presence of AKs in a field of ultraviolet exposure suggests that the field as a whole is prone to develop further such lesions as well as NMSC. Because they can be difficult to distinguish from early invasive SCCs and because their chances of progression to the SCC phenotype cannot be gauged reliably, AKs should be treated, using local and/or field-directed approaches. Monitoring and treatment of AKs should be conducted according to the recommendations described in Table 1. Treatment options for AKs are shown in Figure 1.

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