

Current perspective on actinic keratosis: a review

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Summary

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Actinic keratoses (AKs) are common, with prevalence in the U.S.A. estimated at almost 40 million in 2004 and annual costs of > \$1 billion (U.S.D.). However, there is no universally accepted definition of AK and thus it is difficult to identify reliably. AKs are lesions of epidermal keratinocytic dysplasia that result from chronic sun exposure and have the ability to progress to invasive squamous cell carcinoma (SCC), but clinicians disagree about whether AKs are premalignant lesions, superficial SCC in situ or epiphenomena of chronically sun-damaged skin. Yearly AK to SCC progression rates of 0-6% were reported in an elderly population with multiple prior keratinocyte carcinomas (KCs); and rates of spontaneous AK regression have been reported to be > 50%, but regressed lesions often reappear. As AKs have both cosmetic consequences and potential for malignant transformation, there are multiple reasons for treatment. There is no current agreement on the most efficacious treatment, but 5-fluorouracil has been shown to both prevent and treat AKs, and imiquimod and photodynamic therapy may have the best cosmetic outcomes. AKs may be treated to improve appearance and relieve symptoms, but the keratinocytic dysplasia that gives rise to malignancy, and sometimes appears as an AK, may be what actually threatens patient health. Thus, treatments should aim to decrease the risk of KC or facilitate KC diagnosis by reducing the potential for misidentification created when a KC appears in a field of AKs. Improved agreement among clinicians on AK definition may improve management.

What's already known about this topic?

- Actinic keratoses (AKs) are a major public health concern because of their high prevalence, substantial cost and potential for progression to keratinocyte carcinoma, particularly squamous cell carcinoma.

What does this study add?

- Improved agreement among healthcare practitioners on AK definition and classification is needed to improve management.
- More head-to-head comparisons of alternative treatment strategies for AK are needed to determine the best treatment.

Actinic keratoses (AKs) are diagnosed at > 10% of dermatology visits,¹ making them one of the most common diagnoses seen in the outpatient setting. In 2004, in the U.S.A., AK prevalence was estimated at almost 40 million,¹ with annual costs > \$1 billion (U.S.D.). AKs are problematic because they can develop into keratinocyte carcinoma (KC), leading to serious health consequences. KC includes squamous cell

carcinoma (SCC) and basal cell carcinoma (BCC) of the skin, which are the most common cancers in the U.S.A. and other countries with predominantly light-skinned populations.¹ AKs are a major public health concern because of their high prevalence, substantial financial impact, and potential for malignant transformation. This review discusses the definitions, classification systems, epidemiology, disease course, risk factors,

burden of disease, prevention, treatment and implications of AK. To conduct this review, a search was done in PubMed for English-language publications, using the search terms 'actinic keratosis', 'keratinocyte carcinoma', 'epidemiology' and other related terms, from 1985 to 2015. Clinically relevant articles were selected for review at the discretion of the authors.

Diagnosis and classification

Despite being incredibly common, there is no universally accepted definition of AK and thus it is difficult to identify reliably. Board-certified dermatologists with a mean of 20 years of clinical experience reported significantly different AK counts in the same patients, but improved with consensus discussions.^{2,3} Additionally, many primary care providers are unfamiliar with AKs.⁴

Clinicians agree that AKs are lesions of epidermal keratinocytic dysplasia that result from chronic ultraviolet (UV) radiation exposure and have the ability to progress to invasive SCC,⁵ but specific classification systems vary. Some identify AK as a premalignant lesion distinct from SCC, as many regress and never invade.⁵ Also, AKs and SCCs have been found to express many genes differently—particularly those involved in the mitogen-activated protein kinase pathway.⁶ Others view AK as synonymous with superficial SCC *in situ*, supported by the fact that dysplastic keratinocytes of AK have similar features to those of invasive SCC.⁷ Still others suggest that AKs are epiphenomena of chronically sun-damaged skin arising on the most severely damaged areas,⁸ and that subclinical lesions may be even more prevalent than the ones we see or feel, as confocal microscopy has revealed cellular and nuclear atypical morphology in clinically healthy skin surrounding known AKs.⁹ Additionally, both imiquimod and 5-fluorouracil (5-FU) treatment have been shown to expose visually and treat subclinical AKs by triggering inflammation within them.^{10,11} Several AK classification systems and counting methods have been suggested (Table 1).

Because there is no gold standard for defining AK, the validity of these classifications remains controversial. However, examining the relationship between SCCs and AKs defined in different ways may provide useful insight into the utility of these systems (see 'Course of disease').

Clinically, AKs are described as erythematous or flesh coloured, scaly papules or plaques with a gritty, sandpaper-like texture that is often more easily felt than seen.¹² Some have telangiectasias within or surrounding the lesion, others are heavily pigmented,¹³ and some develop horny proliferations called verrucous keratosis. AKs range in size from a few millimetres to > 2 cm in diameter, often coalesce,⁸ and are usually found in sun-exposed areas such as the face, dorsum of the hands, shoulders and balding scalp. Those on the upper extremities are often thicker and more hyperkeratotic than those on the head and neck. Severe hyperkeratosis can present as a cutaneous horn which reveals a red and fissured base if removed.¹³ Symptoms of AKs include itch and tenderness, but many are asymptomatic.⁸

Histologically, AKs are characterized by atypical keratinocytes with loss of polarity, nuclear pleomorphism and increased mitotic figures in the basal epidermis that may extend into the entire epidermis. Keratinocytes of the sweat glands and hair follicles (acrosvringia and acrotrichia) are spared.⁷ The stratum corneum exhibits alternating parakeratosis and hyperkeratosis secondary to abnormal keratinocyte development,⁷ while keratinocytes in the stratum basale and stratum spinosum appear disordered with pleomorphic and anaplastic nuclei. Many AKs show solar elastosis and a mild inflammatory infiltrate of lymphocytes and plasma cells in the dermis.¹³ Despite these common features, AKs vary histologically, and can, accordingly, be divided into six types: hypertrophic, atrophic, bowenoid, acantholytic, lichenoid and proliferative.¹³

Morphological variation likely affects our ability to diagnose AKs clinically. Multiple studies examined the validity of AK diagnosis by comparing clinical diagnoses with histological readings. Randomly chosen AKs were accurately diagnosed 81% (n = 48) and 91% (n = 22) of the time.^{14,15} Clinically typical AKs were correctly diagnosed 94% (n = 36) and 78% (n = 23) of the time.^{16,17} There are also multiple reports of AKs and BCCs being clinically mistaken for each other.⁵

Frequency

AK is one of the most frequently treated dermatological conditions in the U.S.A. and is more common in men. Because AKs are associated with chronic sun damage, they favour the elderly population and appear almost exclusively in individuals over the age of 45 years, increasing in incidence with age. AK prevalence is higher in warmer climates where populations are exposed to more UV radiation, and in regions where individuals have fairer complexions (Table 2).¹⁸

Course of disease

Actinic keratoses arise as the first clinical sign of abnormal keratinocyte change and then follow one of three paths:⁸ spontaneous remission, stable existence or malignant transformation, with the potential to metastasize.¹⁹ Several studies have attempted to describe the rate of progression of AK to SCC, with numbers ranging from 0.025% to 20% per year,²⁰ and higher rates reported in patients with multiple prior KCs (Table 3).²¹ This variability may, in part, be due to different AK definitions in these studies. Harvey *et al.* report a progression rate of 0% at 1 year in a study of histologically confirmed AKs²²; other studies rely on clinical diagnoses alone and tend to demonstrate greater rates. Marks *et al.* describe specific clinical requirements²³—AKs must have erythema and localized hyperkeratosis with or without telangiectasias or pigmentation. In this study, clinical diagnostic accuracy of AKs was tested before the study and 34 out of 36 (94%) clinically diagnosed AKs were confirmed on biopsy.

Two main pathways of AK progression to invasive SCC have been described. The 'classic pathway' involves the

Table 1 Actinic keratosis (AK) classification systems by clinical and/or histological grade and AK counting systems

Study	Category	Description	Notes
Rossi <i>et al.</i> ¹³	Grade I	Easily visible and slightly palpable	Grading based solely on clinical description may be quite subjective
	Grade II	Easily visible and palpable	
	Grade III	Frankly visible and hyperkeratotic	
Cockerell ²⁴	Grade I	Clinical: pink macule or patch on sun-damaged skin; background mottling; no hyperkeratosis or roughness Histological: lower one-third of the epidermis shows focal atypia of basal keratinocytes	Modelled after cervical intraepithelial neoplasia grading system ²⁵
	Grade II	Clinical: pink/red papule or plaque with rough, hyperkeratotic surface and variable induration Histological: at least the lower two-thirds of the epidermis shows focal atypia of keratinocytes; focal hyperkeratosis, alternating ortho- and parakeratosis; prominent acanthosis and buds of keratinocytes into the upper papillary dermis; upper acrotrichia and acrosyringia may be involved	
	Grade III	Clinical: red, indurated, scaly, sometimes pigmented plaques on sun-damaged skin Histological: atypical keratinocytes spread diffusely throughout the epidermis; parakeratosis, acanthosis, papillomatosis, involvement of adnexal structures	
Röwert-Huber <i>et al.</i> ⁷	Early in situ SCC type AK I	Atypical keratinocytes only in the basal and suprabasal epidermal layers with hyperchromatic, anisokaryotic nuclei that have lost polarity, and sparing of the follicular infundibulum	Based strictly on histopathology
	Early in situ SCC type AK II	Zones of atypical keratinocytes alternate with normal cells (particularly in the acrotrichia and acrosyringia) throughout the lower two-thirds of the epidermis	
	In situ SCC type AK III	Atypical keratinocytes in over two-thirds of the epidermis; adnexal structures are involved	
Goldberg <i>et al.</i> ⁵⁰	Proliferative AK	Clinical: erythematous, scaly macule with ill-defined borders, often > 1 cm in diameter, and potentially reaching 3–4 cm over time; superficial scarring is often seen next to or within the lesion (due to prior treatment) Histological: two-tiered epidermis with lower part composed of anaplastic and monomorphic undifferentiated cells and the upper part keratinized with keratohyalin granules; focal areas of parakeratosis and acanthosis; grows around hair follicles to sebaceous gland level	Based on both clinical description and histopathology
	Nonproliferative AK	Clinical: erythematous, scaly, round, stable macule, usually smaller in size (< 1 cm), does not enlarge and may even disappear Histological: Well demarcated from normal epithelium; usually spares adnexal epithelium	
	Asymptomatic AK (AAK)	Clinical: nontender Histological: fewer infiltrates of T lymphocytes and Langerhans cells than in IAK	
Berhane <i>et al.</i> ²⁹	Inflamed AK (IAK)	Clinical: erythematous halo around lesion, tender to the touch Histological: marked increase in T lymphocytes and Langerhans cells; increase in HLA-DR-bearing cells	As tumours progress from AAK to IAK to SCC, there is a step-wise loss of differentiation, an increase in immunoreactive p53 (suggesting an increase in DNA damage during the inflammatory phase), an increase in the apoptosis inhibitor Bcl-2, and a decrease in Fas and Fas ligand (cells become less sensitive to Fas-mediated apoptosis as they progress). The increase in HLA-DR-bearing cells in IAK suggests an active inflammatory or immune response
	SCC	Clinical: typical SCC features—scaly, erythematous papule, nodule, or plaque that may ulcerate, itch or bleed Histological: fewer infiltrates of T lymphocytes and Langerhans cells than in IAK; more Bcl-2-expressing tumour cells than in AAK	

(continued)

Table 1 (continued)

Study	Category	Description	Notes
Chen <i>et al.</i> ⁵¹	Clinical categories	Discrete erythematous AK	No significant agreement between raters before consensus discussion, 43% agreement after
		Hypertrophic AK	54% agreement between raters before consensus discussion, 18% after
		Nonerythematous AK	No significant agreement between raters before or after consensus discussion
	Methods of counting AKs	Small AK (< 0.25 cm)	No significant agreement between raters before consensus discussion, 21% agreement after
		Large AK (> 0.25 cm): not significantly reliable among raters before consensus discussions	No significant agreement between raters before consensus discussion, 62% agreement after
		Total count (AK of any size): greatest interrater reliability both pre- and postconsensus discussions BSA method: raters mentally combined AKs into a contiguous grouping of lesions and compared this with the size of the patient's palm, representing 1% BSA	18% agreement between raters before consensus discussion, 66% after No significant agreement between raters before or after consensus discussion

SCC, squamous cell carcinoma; HLA-DR, human leucocyte antigen D-related; Bcl-2, B-cell lymphoma 2; BSA, body surface area.

Table 2 Actinic keratosis (AK) prevalence by geographical region

Study	Location	Overall prevalence	Prevalence in men	Prevalence in women
Bickers <i>et al.</i> ¹	U.S.A.	39.5 million people affected in 2004	NA	NA
Neidecker <i>et al.</i> ¹⁸	U.S.A.	5.9 million office visits in 2005	59% of office visits	41% of office visits
Flohil <i>et al.</i> (the Rotterdam Study) ³¹	The Netherlands	21% with 1–3 AKs 9% with 4–9 AKs 8% with ≥ 10 AKs	49% of men aged > 45 years	28% of women aged > 45 years
Frost and Green ⁵²	Review of several locations	< 10% of white adults aged 20–29 years (northern and southern hemispheres) ~ 80% in white adults aged 60–69 years (northern and southern hemispheres)	NA	NA
	Northern Hemisphere	11–25% in the northern hemisphere	25% of outdoor workers in Maryland, U.S.A., aged ≥ 21 years	NA
	Australia	40–60% of adults	27% of men aged 16–49 years 66% of men aged 50–86 years	13% of women aged 16–49 years 56% of women aged 50–86 years
Frost <i>et al.</i> ¹⁵	Australia	46% of adults aged 30–69 years	55% of men aged 30–69 years	37% of women aged 30–69 years
			22% of men aged 30–39 years	8% of women aged 30–39 years
			83% of men aged 60–69 years	64% of women aged 60–69 years

NA, not applicable.

presence of atypical keratinocytes in the lower one-third of the epidermis—keratinocyte intraepidermal neoplasia (KIN I)—advancing to fill the lower two-thirds (KIN II) and then full thickness (KIN III) of the epidermis before becoming invasive

SCC,²⁴ similar to the progression of cervical intraepithelial neoplasia (CIN) associated with human papilloma virus (HPV).²⁵ The 'differentiated pathway', which may be more aggressive and more common, does not require such full-

thickness atypia for malignant transformation. Rather, invasive SCC can arise directly from atypical basilooid cells in the lower one-third of the epidermis, without involvement of the above epidermis, possibly by advancing along hair follicles and sweat ducts.²⁶

In one study, two-thirds of SCCs and one-third of BCCs were shown to arise from previously clinically diagnosed AKs in a high-risk population.⁵ Pathogenesis of the transformation of AK to BCC has not been described, but some KCs contain features of both BCC and SCC.^{27,28} This relationship could also be due to misidentification of BCC as AK, which has been reported.⁵

Although we cannot reliably predict which AKs will progress to invasive carcinomas, signs of progression include induration, inflammation, larger size (> 1 cm in diameter), rapid growth, bleeding, erythema and ulceration of the lesion.²⁰ Because there is no precisely defined clinical boundary between AK and invasive SCC, biopsies are typically performed on lesions with these features.⁸ The transformation from AK to SCC may be associated with a period of rapid inflammation which subsides upon SCC development, likely due to immunosuppression by the SCC to counteract immunodestruction.²⁹

Spontaneous regression of AKs is very common, in some circumstances > 50% (Table 4). Increased regression rates have been associated with working outdoors for those aged 40–49 and 70–79 years, and may be associated with decreased sun sensitivity.¹⁶

Additionally, AKs have been found to indicate an increased risk for all skin cancers. A study of Medicare recipients found that patients with AK had six times the risk of developing any type of skin cancer (KC or melanoma) than those without AK,³⁰ likely because AK is a sign of extensive sun exposure on vulnerable skin. Another explanation is that dysplasia leading to AK development may simultaneously be occurring in clinically healthy skin and later progressing to skin cancer, supporting the aforementioned idea that AKs are epiphenomena of chronically sun-damaged skin.

Risk factors

Individuals with Fitzpatrick type I or II skin characteristics, such as fair skin, freckles, light-coloured eyes (blue or green) and blonde or red hair, are more likely to develop AKs as they are more sensitive to damage from chronic sun exposure.¹³ The Rotterdam study also found that lighter pigmentation and tendency to sunburn were associated with higher risk of AKs, along with male sex, baldness, age > 70 years, use of sun-protective measures, and history of melanoma or KC, particularly SCC.³¹ Of note, severe baldness was most strongly associated with AKs, but only in men. History of smoking was weakly associated with AKs, and naevi, outdoor work history and educational level were unrelated to AK risk.³¹ Immunosuppressive therapy has also been linked to an increased risk

Table 3 Progression rates of actinic keratosis (AK) to squamous cell carcinoma

Study	Progression rate at 1 year (%)	Progression rate at 4 years (%)	Comments
Criscione <i>et al.</i> ⁵	0.60	2.57	Elderly, multiple prior keratinocyte carcinomas
Wulf <i>et al.</i> ⁵³	0	NA	Immunosuppressed organ transplant recipients, mean age 57 years
Callen <i>et al.</i> ⁵⁴	0.25–20	NA	NA
Harvey <i>et al.</i> ²²	0	0	U.K. cohort, mean age 71.2 years, 23% had AKs at baseline
Marks <i>et al.</i> ²³	0.075	NA	Australian cohort, aged ≥ 40 years, mean age 60 years, at least one AK at baseline

NA, not applicable.

Table 4 Regression rates of actinic keratosis (AK) in community-based populations

Study	Percentage of AKs that regressed	Period of time for regression	Participants in study (n)	Mean number of lesions ^a	Total number of lesions ^b	Comments
Criscione <i>et al.</i> ⁵	55	12 months	169	46	7784	Elderly, multiple prior keratinocyte carcinomas
Werner <i>et al.</i> ²¹	29.7	11 months	27	23.5	635	Patients with extensive sun damage (only abstract available)
Frost <i>et al.</i> ¹⁵	76	12 months	96	11.5 in affected patients	494	Australian cohort, aged 25–75 years
Harvey <i>et al.</i> ²²	21	12–24 months	560	1.9 in affected patients	239	South Wales cohort, aged ≥ 60 years
Thompson <i>et al.</i> ¹⁴	25 (sunscreen) 18 (placebo)	7 months	431	8.1	3498	Australian cohort, aged ≥ 40, at least one AK at baseline
Marks <i>et al.</i> ²³	25.9	12 months	618	7.7	4759	Australian cohort, aged ≥ 40 years, at least one AK at baseline

^aMean number of lesions per person; ^bTotal number of lesions in the study.

of AK.⁷ However, unlike in Merkel cell carcinoma and other cancers associated with immunosuppression which have been linked to viral infections, no virus has been consistently associated with increased risk of AK.³²

Some reports suggest that HPV infection may increase risk of both primary AK and recurrent AK following therapy.³³

UVB radiation (wavelength 290–320) is a major factor in AK formation, as it creates mutations by forming thymidine dimers in the DNA and RNA of keratinocytes.⁷ Alteration of p53 and its pathways can result in unregulated proliferation of dysplastic keratinocytes, leading to AK and SCC formation.

Jacobs *et al.* show that genetics may play a role independent of skin colour.³⁴ The authors performed a genome-wide association study of the Rotterdam population and found that IRF4, MC1R and TYR likely work together to increase AK risk by affecting pigmentation and oncogenic functions.

Burden of disease

Because AK is not a fatal condition it is important to understand its morbidity, particularly the effects on quality of life. Cross-sectional analyses showed that higher AK counts are associated with worse skin-related quality of life in a population with a history of KC.^{35,36} However, prospective analyses found that as individuals developed new AKs over time, their skin-related quality of life did not change, suggesting that AK count may be an indicator rather than a cause of worse skin-related quality of life.³⁶ For example, AKs are a common feature of actinic neoplasia syndrome (ANS), a chronic condition associated with worse skin-related quality of life. ANS is defined by a history of at least two KCs in the last 5 years,³⁵ and may be associated with worries of future skin cancers, increased visits to the dermatologist and constant awareness of the need to protect oneself from the sun.

Because AKs are so common in the population and are typically treated to lower the risk of progression to SCC, they create a substantial financial burden on our healthcare system. In 2004, direct costs of AKs in the U.S.A. were estimated at \$1.2 billion per year,³⁷ and indirect costs reached almost \$300 million.¹⁸ Over 90% of direct costs are attributed to physician office visits, while only 7% are attributed to prescription drugs.³⁷ These office visit costs include the cost of destructive procedural treatment, which is done > 10 times more frequently than topical medication.³⁸ Because AK treatments are so commonly performed, cost is an important factor. In a Medicare population, the average visit for removal of an AK by destruction was estimated at \$131 and a visit involving prescription of a topical medication was estimated at \$181, using data from the Medicare Current Beneficiary Survey from 1998 to 2000.³⁸

Prevention of actinic keratoses

Preventative efforts are potentially cost-effective, may reduce concern about malignant lesions and may avoid treatment side-effects. Multiple studies highlight the effectiveness of sunscreen use which has a dose-dependent effect on decreasing

the development of new AKs, as well as increasing the remission rate of existing lesions.^{14,39} Other efforts to decrease UV radiation exposure such as advocating safe sun practices, reducing use of indoor tanning beds and wearing protective clothing such as hats and long sleeve shirts are presumed to be effective, particularly when employed consistently.¹⁸

Chemoprevention of actinic keratoses

Topical therapies, such as 5-FU, may prevent the development of new AKs. In a population with multiple prior KCs, a single month-long course of topical 5-FU was shown to reduce the number of AKs and subsequent AK treatments for > 2 years,⁴⁰ and to reduce the number of new AKs (J.L. Walker, J.A. Siegel, M. Sachar, H. Pomerantz, S.C. Chen, S.M. Swetter, R.P. Dellavalle, G.P. Stricklin, A.A. Qureshi, J.J. DiGiovanna, M.A. Weinstock, For the VAKCC Trial group, unpublished data).

Treatment of actinic keratoses

Treatment for AK primarily consists of lesion-directed destruction or field treatment with topical medications which aim to prevent progression to KC, as well as improve appearance and relieve symptoms. Therapies and adverse effects (local and systemic) are listed in Table 5.

A recent network meta-analysis, which evaluated AK therapies based on complete clearance rates, ranked topical treatments from highest efficacy to lowest efficacy as follows: 5% 5-FU; 0.5% 5-FU; photodynamic therapy (PDT) with aminolaevulinic acid (ALA); imiquimod; ingenol mebutate and methyl aminolaevulinate PDT (MAL-PDT); cryotherapy; diclofenac with hyaluronic acid; placebo.⁴¹ However, a different network meta-analysis found that PDT with a stable nanoemulsion-based ALA formulation (BF-200 ALA) had better clearance rates than 5-FU and that imiquimod (16 week dose) worked better than ALA-PDT.⁴² A 2012 Cochrane review of 83 different randomized controlled trials found that field therapy with diclofenac, 5-FU, imiquimod, and ingenol mebutate all had similar efficacies, and no data were found on the relationship between different AK treatments and decreased rates of SCC.⁴³ Additionally, high-dose topical tretinoin has not been effective in AK prevention. Systemic retinoids are avoided owing to a significant side-effect profile.⁴⁴ These findings show that there is no current agreement on the best field treatment for AK.

For lesion-directed treatments, the Cochrane Review reported that PDT was more effective than cryotherapy.⁴³ However, such therapies may vary with technique. A study of liquid nitrogen cryotherapy found that longer freeze times improved 3-month AK clearance rates, with 39% success after freezing for ≤ 5 s, 69% success after freezing for ≥ 5 s and 83% success after freezing for at least 20 s.⁴⁵

Combinations of spot treatments and field therapies may be more effective than spot treatment alone. One study compared treatments of cryotherapy combined with either 0.5% FU cream or a placebo vehicle cream and found that the group

Table 5 Local and systemic adverse effects of actinic keratosis (AK) treatments⁵⁵

Treatment type	Treatment	Local adverse effects	Systemic adverse effects	Notes
Lesion-directed therapy	Liquid nitrogen cryotherapy ⁵⁶	Short term: pain, oedema, blistering, infection, pyogenic granuloma (rare) Long term: nerve damage, pigment changes	NA	NA
	CO ₂ laser resurfacing ^{57,58}	Persistent erythema, dyspigmentation, infections, scarring	NA	NA
	Curettage ⁵⁹	Scar, infection, vital structure damage (rare)	Reactivation and local spread of HSV	Works well for hyperkeratotic lesions
	Dermabrasion ⁶⁰	Intense pain	NA	Used for large areas such as scalp or forehead; usually requires procedural sedation and analgesia
Topical field treatment	5-FU ⁶¹	Erythema, inflammation, erosions, pain, pruritus, photosensitivity, burning	Headache, insomnia, irritability, stomatitis, leucocytosis, thrombocytopenia, birth defects, herpes simplex reactivation, miscarriage, neutropenia, neurotoxicity, gastrointestinal toxicity	Systemic toxicity mostly seen in patients with dihydropyrimidine dehydrogenase deficiency; not recommended in patients with melasma or acne rosacea
	Imiquimod ⁶¹	Erythema	Upper respiratory tract infection, influenza-like symptoms, HSV	NA
	Ingenol mebutate ^{61,62}	Pain, itching, irritation, infection, dose-related erythema, flaking/scaling/dryness, scabbing/crusting	Headache, periorbital oedema, nasopharyngitis, conjunctivitis, eye pain, herpes zoster, severe hypersensitivity (rare)	FDA warning about systemic adverse effects was issued in August 2015 ⁶³
Lesion-directed or field therapy	Diclofenac ^{61,64}	Dry skin, pruritus, erythema	Hepatotoxicity (rare)	NA
	Photodynamic therapy ⁴³	Burning or stinging during light exposure, pigmentary changes	NA	FDA approved for lesion-directed treatment but is used off label as field therapy

NA, not applicable; HSV, herpes simplex virus; 5-FU, 5-fluorouracil; FDA, Food and Drug Administration.

using 0.5% FU had a significantly greater decrease in AKs compared with the placebo group 6 months after treatment.⁴⁶ Another study found that cryotherapy with imiquimod was more effective than cryotherapy alone in treating individual lesions, as well as reducing overall AK count.⁴⁷

Although the treatment with the best efficacy is controversial, certain therapies may be preferred for cosmetic reasons. In a review of several randomized controlled trials and split-face studies, imiquimod and PDT were shown to have better cosmetic outcomes than 5-FU, trichloroacetic acid, diclofenac sodium, ingenol mebutate, surgical procedures and laser therapy. Also, MAL-PDT had a better cosmetic outcome when preceded by microneedling compared with MAL-PDT alone.⁴⁸ Efforts to ameliorate adverse consequences of these treatments are important, as patient satisfaction, which may affect compliance, is not only based on treatment efficacy, but also on pain, discharging ulcers, and other factors associated with topical therapies.⁴⁹

Implications and conclusions

Although there is no universal definition of AK, these lesions are common, commonly treated and associated with enormous

costs. As life expectancy increases, AK and other conditions related to lifelong UV exposure are likely to increase,¹⁸ placing further strain on the healthcare system. Huge amounts of resources are currently devoted to AK management. As AKs have both cosmetic consequences and potential for malignant transformation, there may be multiple reasons for treatment. AKs are a considerable cosmetic problem, as > 80% appear on visible parts of the body such as the head, neck, dorsal surface of the hands and forearms,⁴⁸ and they may negatively impact quality of life. Therefore, many patients desire treatment to improve appearance and relieve symptoms. However, it may be that the keratinocytic dysplasia that gives rise to malignancy, and sometimes appears as an AK, is what actually threatens patient health. To address this issue, AK treatments should aim to decrease the risk of KC development or facilitate KC diagnosis by reducing the potential for misidentification created when a KC appears in a field of AKs. More head-to-head comparisons of AK treatment strategies are needed and their efficacy should be evaluated based on both prophylaxis against malignancy and cosmetic goals. Additionally, improved agreement among healthcare practitioners on AK definition and classification may improve management. Although the percentage of

misdiagnosed AKs is small, a large number of people are affected, given their high prevalence. Finally, a better understanding of the progression of AK to KC might allow for better management of AKs, lowering costs and morbidity associated with treatment side-effects.

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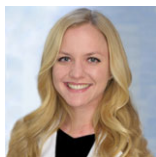
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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Video S1. Author video.



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