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Guidelines for the management of actinic keratoses

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Summary

These guidelines stemmed from a consensus meeting held by the British Photobiology Group (BPG) in 1999. Following this meeting one of the authors (J.M.M.) was invited to draw up guidelines for the management of actinic keratoses by the British Association of Dermatologists Therapy Guidelines and Audit Subcommittee. Relevant evidence was sought using the search terms 'solar keratosis' and 'actinic keratosis' in Medline from 1966 onwards. Additional and earlier literature was reviewed on the basis of references within post-1966 publications. All articles of apparent relevance were reviewed independently of the nature of the publication. The quality of the evidence elicited has been indicated. The National Ambulatory Medical Care Survey (U.S.A.) was used for further data on topical chemotherapy. Papers were reviewed and discussed by the contributors to the BPG Workshop (see Acknowledgments). Recommendations are evidence based where possible. Strength of recommendation is coupled with quality of evidence. Strength of recommendation includes consideration of apparent cost-benefit and practical considerations. Quality of evidence reflects the nature of the trial structure that provides data of efficacy.

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Disclaimer

These guidelines have been prepared for dermatologists on behalf of the British Association of Dermatologists (BAD) and reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. Just as adherence to the guidelines may not constitute defence against a claim of negligence, so deviation from them should not necessarily be deemed negligent.

Methodology

These guidelines stemmed from a consensus meeting held by the British Photobiology Group (BPG) in 1999. Following this meeting one of the authors (J.M.M.) was invited to draw up guidelines for the management of actinic keratoses (AKs) by the BAD Therapy Guidelines and Audit Subcommittee. Medline (1966–2004) was the main source of references for this review. Relevant evidence was sought using the search terms 'solar keratosis' and 'actinic keratosis'. Additional and earlier literature was reviewed on the basis of references within post-1966 publications. All articles of apparent relevance were reviewed independently of the nature of the publication. The National Ambulatory Medical Care Survey (U.S.A.) was used for further data on topical chemotherapy. Papers were reviewed and discussed by the contributors to the BPG Workshop (see Acknowledgments).

Definition and introduction to the guideline

Actinic (syn. solar) keratoses are keratotic lesions occurring on chronically light-exposed adult skin. They represent focal areas of abnormal keratinocyte proliferation and differentiation that carry a low risk of progression to invasive squamous cell carcinoma (SCC). A spectrum of histology is seen but the cardinal feature of an AK is epithelial dysplasia. This may be restricted to the basal layer or may extend to full-thickness atypia at which point differentiation from Bowen's disease can be difficult. There is disorderly arrangement and maturation of epithelial cells. Multiple buds of epithelial cells may occur at

the membrane zone but no invasion is seen. Histological variants of AK have been described, including hypertrophic, bowenoid, lichenoid, acantholytic and pigmented.

AKs are widely considered to be premalignant lesions with low individual potential for invasive malignancy and higher potential for spontaneous regression. They present as discrete, sometimes confluent, patches of erythema and scaling on predominantly sun-exposed skin, usually in middle-aged and elderly individuals. They are often asymptomatic but may occasionally be sore or itch. Lesions may be single or multiple. The epidemiology, risk factors, disease associations and demographics of the 'at-risk' population are all pertinent to patient management. They are discussed together with the available treatment options.

Epidemiology

Evidence suggests that most AKs are the result of chronic exposure to ultraviolet (UV) radiation. They occur predominantly on chronically sun-exposed skin, such as that of the face and dorsa of hands, in fair-skinned individuals.[1] In addition, UVB-specific p53 mutations have been demonstrated in AKs, providing molecular evidence in support of a role for sunlight.[2] There is a high prevalence in those receiving chronic immunosuppression

Table 1 Factors determining choice of active therapy from six main alternatives. The scoring is based on the authors' evaluation of efficacy, ease of use, morbidity and cost-benefit

	Cryosurgery	5-FU	Diclofenac	Imiquimod[a]	Curettage	PDT	Comments
Main characteristic of AKs							
Low number of AKs	●●●●	●●●●	●●	●●	●	●	
High number of AKs	●●●	●●●●	●●●	●●●	●	●●●	
Thin AKs	●●●	●●●●	●●●	●●●	●	●●	Thin lesions may not always require treatment
Hypertrophic AKs	●●	●	●	●	●●●●	●	Histology may be required. Formal excision may be preferred
Isolated lesions failing to respond to other therapies	●●	●	●	●	●●●●	●	Histology may be required. Formal excision may be preferred
Confluent recalcitrant AKs, failing other treatments	●●●	●●●	●	●●●	●	●●●	Certain lesions within a resistant field may require histological assessment
Location							
Scalp, ears, nose, cheeks, forehead, perioral	●●●●	●●●●	●●●	●●●●	●●●	●●●	
Periorbital	●●●	●	●	●	●●●	●●●	Topical therapies can be difficult to use near mouth and eyes
Confluent scalp	●●●	●●●●	●●●	●●●●	●	●●●●	Pretreatment with 5% salicylic acid ointment may improve outcome
Below the knee	●●●	●	●●	●	●●●●	●●●●	Poor healing is a particular concern at this site. All modalities can lead to ulceration. Treatment may be combined with advice on elevation and compression bandaging where possible
Back of hands	●●●●	●●●●	●●	●	●●●	●●●	Courses of topical therapy may need to be extended and pretreatment with 5% salicylic acid ointment may improve outcome
Characteristics of patient (rating may be considered in context of clinical need indicated by characteristic of AK and location)							
Medically dependent or senile	●●●	●●	●●●	●	●	●●●	Morbidity of treatment may dictate choice of modality
Self-reliant	●●●	●●●●	●●●	●●●●	●	●	5-FU may be repeated at sites of relapse or new lesions in primary care
One-off treatment	●●●●	●●●●	●	●●●●	●●●	●●●	
Lives far from hospital	●●●	●●●●	●●●	●●●●	–	–	May favour treatment that allows monitoring in primary care
Part of continuous management plan	●●●●	●●●●	●●●	●	●	●●●	

5-FU, 5-fluorouracil; PDT, photodynamic therapy; AKs, actinic keratoses; ●●●●, good treatment; ●●●, fair treatment, ●●, can be used depending on circumstances; ●, rarely used in these circumstances. [a]Imiquimod is not currently licensed for use in the treatment of AKs.

as organ transplant recipients.[3] Other possible risk factors include exposure to arsenic[4,5] and chronic sun bed use.[6–8]

Incidence and prevalence

In Ireland and the U.K., 24%, 23% and 19% of individuals aged over 60 years were found to have at least one AK in studies from Galway, South Wales and Merseyside, respectively.[9–11] There was a linear increase in the prevalence with age (from 60 to 80 years) in men but not in women, and the rate of new AKs was estimated to be 149 per 1000 person-years.[10] AKs were also present in 3·6% of men aged between 40 and 49 years.[11]

Natural history: spontaneous regression and malignant transformation

Studies indicate a high spontaneous regression rate in the order of 15–25% for AKs over a 1-year period,[10,12] and a low rate of malignant transformation, less than one in 1000 per annum.[13] None the less, mathematical models derived from this study predict that for an individual with an average of 7·7 AKs, the probability of at least one transforming within a 10-year period is approximately 10%.[14]

When 918 adults (mean age 61 years) with AKs but no previous history of skin cancer were followed prospectively for 5 years, the incidence rate for basal cell carcinoma (BCC) and SCC was estimated at 4106 and 3198 per 100 000 person-years, respectively, representing a substantial excess incidence compared with the general population.[15] These data suggest that even though the risk of malignant transformation for any given AK is very low, the probability of an individual with AKs presenting subsequently with skin cancer is none the less high compared with the population at large.

Investigation and diagnosis

Patients with AKs may present to dermatologists in various circumstances: they may be referred by the general practitioner (GP) because of diagnostic uncertainty or concern about malignant risk or for further management, and AKs may be detected incidental to referral for another problem, or detected during follow up of a skin cancer patient. Diagnosis is frequently made on clinical appearance alone but as the differential diagnosis includes superficial BCC, Bowen's disease, invasive SCC and even amelanotic melanoma, a skin biopsy may be indicated in selected cases where there is clinical doubt or suspicion of invasive malignancy.

Management

Many options are open to patients with AKs. The natural history of individual lesions studied in the U.K. suggests that treatment is not universally required on the basis of preventing progression into SCC.[10] However, others feel that prevention of SCC is the main reason for therapy.[16]

Some AKs have histological features within the spectrum of *in-situ* skin cancer. They can also represent a cause of symptoms and disfigurement which may be the main determinant of treatment choices. Clinical judgement should discern which lesions are more likely to represent a risk to the patient's health, but where the likelihood is low, options include no therapy or palliation with emollient or keratolytic agent such as low-strength salicylic acid ointment.

Where active treatment is sought, many modalities of therapy are available (Table 1). Good-quality data on the outcome of these different therapies are available in only a few instances. Treatment of an individual lesion may have a therapeutic effect on surrounding skin, with an effect on overall progression of actinic damage, but this potential benefit has not been quantified. Given the low morbidity and risk of the majority of AKs, the *Strength of recommendation* (see Appendix 1) made for treatments by the authors has an element of cost-benefit and risk-benefit included. This is derived from clinical experience in addition to the published evidence.

No therapy (*Strength of recommendation A, quality of evidence II-ii*)

Harvey *et al.*[10] reported in a study of 560 individuals from Wales that 21% of AKs resolved spontaneously over a 12-month period and none progressed into SCC. Marks *et al.*[13] reported the evolution of AKs in an Australian cohort, where malignant transformation was quoted at 0·075–0·096% of AKs per year.

Topical therapies

- No therapy (*A*, II-ii) or emollient (*A*, I) is a reasonable option for mild AKs
- Sun block applied twice daily for 7 months may protect against development of AKs (*A*, I)
- 5-Fluorouracil cream used twice daily for 6 weeks is effective for up to 12 months in clearance of the majority of AKs. Due to side-effects of soreness, less aggressive regimens are often used, which may be effective, but have not been fully evaluated (*A*, I)
- Diclofenac gel has moderate efficacy with low morbidity in mild AKs. There are few follow-up data to indicate the duration of benefit (B, I)
- Imiquimod 5% cream is not licensed for AKs, but has been demonstrated to be effective over a 16-week course of treatment but only 8 weeks of follow up. By weight, it is 19 times the cost of 5-fluorouracil. They have similar side-effects (B, I)

Emollient (*Strength of recommendation A, quality of evidence I*)

There are no trials dedicated to the study of palliative therapy of AKs but emollient has been employed in the placebo arm

of a double-blind trial of masoprocol cream.[17] Forty subjects were in the vehicle placebo group, with an average of 13·4 AKs each falling to 11·1 after 28 days of emollient twice a day. This represented improvement in the global evaluation score in 44% of subjects, with only 2·4% showing a deterioration. The vehicle limb of a randomized trial of diclofenac gel in hyaluronan vehicle described resolution of the target lesion in 44% of subjects using the vehicle after 60 days.[18] Follow-up data are lacking and it is likely that the treatment is managing the clinical manifestations of mild AKs rather than reversing biological processes.

Sun block (*Strength of recommendation A, quality of evidence I*)

Sun block has a combined emollient and photoprotective effect. A randomized placebo-controlled trial of sun block with factor 17 protection applied twice daily to the face for 7 months showed sun block to be superior to emollient in terms of total number of AKs and new lesions at the end of the trial.[19] A single daily application of sun block (sun protection factor 16) in Queensland, Australia, showed it to be superior to discretionary use of the same sun block over a 2-year period in the reduction of AKs.[20] A similar approach in the same setting also reduced the incidence of cutaneous SCCs.[21]

Salicylic acid ointment (*Strength of recommendation A, quality of evidence III*)

Salicylic acid ointment is sometimes used as a preliminary to topical 5-fluorouracil (5-FU) to remove overlying keratin. Fifty per cent salicylic acid in croton oil has been described as a treatment for AKs when used in combination with 20% trichloroacetic acid (TCA) and pretreatment with topical tretinoin as a serial regimen for facial peel.[22] Acting primarily as an emollient for mild keratoses[17,18] (see above under Emollient), it may provide a small additional benefit based on the keratolytic effect. Thus 2% salicylic acid ointment BP may be used for its combined emollient and mild keratolytic effects, either alone or as pretreatment for topical 5-FU.

5-Fluorouracil (*Strength of recommendation A, quality of evidence I*)

The majority of the data on topical therapies relates to 5-FU. A wide range of open trials, dose-ranging studies and manipulations of the vehicle has been reported over the last 35 years, as well as two randomized controlled trials (RCTs), confirming efficacy. 5-FU works by the inhibition of thymidylate synthetase, which is needed for DNA synthesis. It may also interfere with the formation and function of RNA.[23]

Nine of the trials were controlled, where a right/left comparison ($n = 6$) was the most common design, but only five were randomized. Numbers in the studies were generally small, with a mean of 26 patients per trial and fewer than 15 patients in 50% of trials. Minimum follow up was 12 months or more in only two studies. Many open studies appeared to demonstrate the efficacy of 5-FU in a range of potencies and different vehicles in the treatment of AKs when used on the face twice daily for 3 weeks. Only two trials studied the use of 5-FU in the currently available formulation of a 5% cream in a well-constructed, controlled manner.[24,25] Kurwa *et al.*[25] examined the lesional area of AKs on the back of the hands before and after treatment with 5% 5-FU cream twice daily for 3 weeks in a randomized right/left comparison with a single treatment with photodynamic therapy (PDT). Of the 14 patients evaluable at 6 months, there was a mean reduction in lesional area of 70% (5-FU) and 73% (PDT), with no statistically significant difference between them. Open studies have suggested that this regimen is not sufficiently long for effective treatment of AKs on the hands,[26] but is adequate for those on the face.[24] Witheiler *et al.*[24] used 5% 5-FU cream on the face as control in a right/left comparison with a single application of Jessner's solution (14% lactic acid, 14% salicylic acid, 14% resorcinol in ethanol) followed by a 35% TCA peel. There was a mean reduction in AKs on both sides of the face from 18 to four (78% reduction with 5-FU and 79% reduction with TCA). This benefit was sustained for 12 months. The third follow up at 32 months demonstrated that the number of AKs had risen again to 10 (5-FU) and 15 (TCA) in the eight evaluable patients. These differences were not statistically significant.

The results of using the same formulation of 5-FU less frequently, but for prolonged periods, are conflicting. An open trial of 10 patients reported clearance of 96% of AKs after a mean of 6·7 weeks applying treatment twice daily, once or twice per week.[27] Six patients were followed for 9 months and showed an 86% clearance rate that was maintained. Epstein[28] followed this study with a similar protocol and sample size, except that evaluation was done by dermatologists given a series of photographs and blinded as to the sequence. Eight of 13 patients failed to show any improvement, with the conclusion that pulsing 5-FU over a period of < 10 weeks is not effective. The small numbers of patients in both these studies leave the matter unresolved. Five per cent 5-FU cream was used alone or in combination with topical tretinoin to the back of the hands at night for 3 months in a blinded right/left comparison with a 3-month follow-up period.[29] Both sides produced a reduction of $> 70\%$ in AKs, with a statistically significant advantage to the side treated with additional tretinoin.

Imiquimod 5% cream (*Strength of recommendation B, quality of evidence I*)

Imiquimod 5% cream is a topical immune response modifier. A small early RCT against vehicle placebo[30] demonstrated clearance rates of 84% when used up to three times per week for 12 weeks. There have been two RCTs[31,32] with regimens of three times per week for 16 weeks and follow up 8 weeks later. These have classified responses in terms of complete or partial ($> 75\%$) clinical clearance or histological clearance.

Results indicated 47% of patients with complete clearance (vs. 7·2% with placebo) increasing to 64% when adding those with partial clearance (vs. 13·6% with placebo).[31] Histological responses were 57% (vs. 2·2% for placebo) and 72% (vs. 4·3% for placebo) for the same categories.[32] The side-effects are similar to 5-FU with severe erythema (30·6%), scabbing and crusting (29·9%) and erosions or ulceration (10·2%).[32] The extent of side-effects is not wholly predictable, with some patients manifesting an extreme reaction and others very little. The clinical response is largely in proportion to the side-effects and those terminating treatment early due to extreme soreness may still get a good response. There are limited long-term data on relapse after treatment. The product is not currently licensed for this indication and imiquimod is more expensive than 5-FU, gram for gram, by a factor of 19.[33]

Diclofenac gel (*Strength of recommendation B, quality of evidence I*)

There are two vehicle-controlled studies of 3% diclofenac in a 2·5% hyaluronic gel in the treatment of mild AKs. In the first, patients were treated for a mean of 60 days, with a resolution of 70% of target lesions in the treatment group in comparison with 44% in those using the vehicle.[18] In the second study treatment was for 90 days, with 50% of those using active treatment achieving a target lesion number score of zero, vs. 20% of those treated with vehicle alone ($P < 0{\cdot}001$).[34] Assessment was limited to 30 days post-treatment in both studies. These data provide indication of moderate efficacy with low morbidity in mild AKs. Treatment was well tolerated and side-effects were mainly pruritus (41% estimated after 30 days of treatment) and rash (40% estimated after 60 days).[18]

Tretinoin cream (*Strength of recommendation B, quality of evidence I*)

Topical tretinoin cream has been studied at different concentrations. There is a dose response; Bollag and Ott[35] reported complete clearance of AKs in 55% of subjects treated with 0·3% ointment vs. 35% of subjects with the same response when using 0·1%. Misiewicz *et al.*[36] undertook a right/left comparison of tretinoin cream with arotinoid methyl sulphone on the face, revealing a reduction of AKs on the tretinoin-treated skin by 30·3% ($P < 0{\cdot}01$) after twice-daily use for 16 weeks. At between 3 and 9 weeks there was a deterioration of clinical appearance to below baseline before benefit was seen. This reflects the potential benefit from currently available formulations of tretinoin. In a multicentre open trial, published in nonpeer-reviewed literature, there was a reduction of facial AKs from a mean of 11·2 to 8·9 (11% reduction) after 6 months' use of 0·05% once or twice daily ($P = 0{\cdot}001$). This changed to a reduction by 47% after 15 months' use ($P = 0{\cdot}001$).[37] These figures do not illustrate a significant advantage over emollient and sun block. The product is licensed for photodamage in the U.K., but not specifically for the treatment of AKs.

Masoprocol cream (*Strength of recommendation C, quality of evidence I*)

A single RCT for masoprocol[17] suggested that this reduced AKs to 71% of the baseline number after a 28-day course of therapy. There was only a 1-month follow-up period. The product is not available in the U.K.

In conclusion, there is good evidence that 5% 5-FU cream used twice daily for 3 weeks is effective at reducing AKs on the face and back of hands by about 70% for up to 12 months. There is insufficient RCT evidence to support or refute the efficacy of alternative regimens and formulations, although one RCT suggests that a single night-time application for 3 months for AKs on the back of the hands is effective.[29] Imiquimod has been more rigorously assessed with modern RCT design and may produce a similar pattern of side-effects and response to 5-FU. Diclofenac gel is a relatively mild agent that reduces the AK count but there are no follow-up data beyond 1 month. Topical tretinoin has some efficacy on the face, with partial clearance of AKs, but may need to be used for up to a year at a time to optimize benefit. Sun block, emollient and 2% salicylic acid ointment BP may reduce the AK count by a similar amount.

Other treatments

- Cryosurgery is effective for up to 75% of lesions in trials comparing it with photodynamic therapy. It may be particularly superior for thicker lesions, but may leave scars (*A*, I)
- Photodynamic therapy is effective in up to 91% of AKs in trials comparing it with cryotherapy, with consistently good cosmetic result. It may be particularly good for superficial and confluent AKs, but is likely to be more expensive than most other therapies. It is of particular value where AKs are numerous or when located at sites of poor healing such as the lower leg (B, I)
- There are no studies of curettage or excisional surgery, but both are of value in determining the exact histological nature of proliferative or atypical AKs unresponsive to other therapies, where invasive squamous cell carcinoma is possible

Surgery

There are no trials of surgical therapy for AKs. The nature of the pathology makes it likely that a surgical procedure able to remove an area of diseased skin represents an effective therapy. It is unlikely that this would be a first line of treatment unless there was diagnostic uncertainty. A curettage specimen may make it difficult to determine whether a lesion has an element of dermal invasion. In some instances a deep shave or formal excision with histological examination might be preferred. If curettage is used for a hyperkeratotic AK, it may be warranted to employ two or three cycles of therapy. This will

ensure that if the histology is that of invasive SCC, or if it is equivocal, the curettage is likely to still represent adequate treatment. Exceptions would be where the size, histological type or location of an SCC would make curettage an unacceptable treatment.[38]

In the U.S.A., surgical therapies, including electrodesiccation, are the preferred treatment of AKs provided by dermatologists according to medical insurance data, where 75% are treated by 'either local excision or destruction of lesion or tissue'.[39]

Cryosurgery (*Strength of recommendation A, quality of evidence I*)

A randomized study comparing cryosurgery with PDT in 193 patients indicated an overall 75% complete response rate for cryosurgery in contrast to 69% in those treated with PDT at 3 months.[40] The differential success of the two therapies was more marked for thick lesions, with 69% showing complete response to cryosurgery vs. 52% to PDT. A double freeze–thaw cycle was used in this study in contrast to a single cycle which, when used in a different study, yielded a 68% response.[41]

Extensive cryosurgery over large areas has been referred to as cryopeeling and can be used for treating fields of AKs and background damage.[42] Cryosurgery has been described in combination with topical 5-FU, where the duration of treatment and consequent side-effects of both modalities could be reduced while maintaining efficacy.[43] No data were presented to support this method. Cryosurgery is a flexible therapy that requires skill in administration. With larger doses it is likely to result in loss of pigment and scarring. Patient counselling is important concerning short- and long-term side-effects.

Photodynamic therapy (*Strength of recommendation B, quality of evidence I*)

PDT requires a dedicated light source in combination with the application of a photosensitizing cream. Photosensitizing agents include 5-aminolaevulinic acid (5-ALA) and a methyl ester of 5-ALA, 5-methylaminolaevulinate. The BPG published guidelines for the use of PDT in 2002,[44] and concluded that optimal irradiance, wavelength and dose for the treatment of AKs have yet to be established. For most situations, superficial crust or keratin is first removed with light curettage and the photosensitizing cream then applied under occlusion for 3 h prior to irradiation. Treatment can be painful but the BPG guidelines[44] describe the treatment as intrinsically safe.

Response rates to two cycles of PDT mainly on the scalp and face range from 69% to 91% in three randomized trials.[40,41,45] Studies had a 3[40,45] to 4[41] month follow-up period. In two studies where comparison was made with cryotherapy, one showed a higher clearance rate for cryotherapy (69% PDT vs. 75% cryotherapy)[40] and one showed a lower clearance rate (91% PDT vs. 68% cryotherapy).[41] Cryotherapy appeared to be superior for thicker lesions (PDT response 52·2% vs. cryotherapy 69%) and lesions of the face and scalp (PDT response 75·8% vs. cryotherapy 91·7%). Local adverse reactions were reported by 44% of those receiving PDT and 26% of those given cryotherapy, although the cosmetic outcome in all studies was consistently rated higher by patients for PDT (98%) than for cryotherapy (91%).[40]

A right/left comparison of AK treatment on the back of the hands by PDT and 5-FU showed a similar response to both therapies,[25] clearing 73% and 70%, respectively. Responses remained similar at 6 months.

The cost-effectiveness of PDT is not established but its use is likely to be limited by the cost of the photosensitizing cream.

Laser, chemical peels and dermabrasion (*Strength of recommendation C, quality of evidence III*)

In principle, carbon dioxide laser or other destructive energy sources should be able to treat AKs.[46] Chemical peels and dermabrasion should have a similar effect, where skin is destroyed to a controlled depth. Spira *et al.*[47] reported a poorly controlled comparison of AKs of the face treated with a phenolic peel, dermabrasion or topical 5-FU. All therapies worked initially, but patients developed further AKs within a month of treatment with phenolic peel, within 6 months of dermabrasion and some time after 6 months following 5-FU. The nonblinded right/left comparison by Witheiler *et al.*[24] of a 35% TCA peel and 5-FU on the face suggested that they were of similar efficacy, with improvement sustained up to 12 months, waning considerably by 32 months. TCA can be combined with 70% glycolic acid[48] or with manual dermabrasion with silicon carbide sandpaper.[49]

In an open study of facial dermabrasion alone, 22 of 23 subjects (96%) remained free of AKs at 1 year and the mean period to development of a further AK was 4·5 years.[50] Treatment of scalp actinic damage and keratoses with dermabrasion has been reported as effective.[51]

Systemic retinoids (*Strength of recommendation B, quality of evidence I*)

Systemic retinoids have been assessed for their potential role in suppression or treatment of multiple AKs. Early studies employed etretinate and demonstrated in double-blind crossover trials the efficacy of this drug.[52] Anecdotal evidence over the last 20 years suggests that there can be some considerable morbidity employing this treatment. In addition, there may be a rebound effect once the systemic therapy is stopped. However, these effects were not observed at 4 months follow up in the one available report on this subject.[53]

Use of systemic retinoid may be justified in very high-risk patients, such as organ transplant recipients, where there is a presumed increased risk of progression from AK to SCC.[54] Low-dose acitretin is currently given as a treatment option in

'European best practice guidelines' for renal transplant patients with multiple dysplastic skin lesions.[55]

Site-specific treatments

The data from available treatments indicate that some treatments are more adaptable than others and that morbidity varies with location. The balance of issues determined by location, characteristics of the AKs and nature of the patient are summarized in Table 1. The scoring is based on the authors' evaluation of efficacy, ease of use, morbidity and cost-benefit.

Other considerations

Should actinic keratoses be treated?

There is inadequate evidence to justify treatment of all AKs to try to prevent malignant change. Treatment should be considered on an individual basis according to signs, symptoms and history. There will be instances where excision is undertaken for diagnostic purposes.

Overall, the data comparing individual treatments are not good enough to justify making a single recommendation. Decisions for an individual patient will be based on the clinical presentation, the efficacy, morbidity, availability and cost of relevant treatments and patient preference.

However, treatment of small numbers of AKs with cryotherapy is currently widely practised by dermatologists, while more extensive AKs are commonly treated with 5-FU. Due to expense and inconvenience PDT is probably best reserved for patients with extensive AKs that cannot be controlled with other therapies.

Is there a role for prevention and what works?

AKs are a marker for sun damage and therefore are an indication to increase sun-avoidance measures. There is some evidence that regular use of sunscreen reduces the number of AKs[19,20] and the risk of SCC.[21]

Should patients with actinic keratoses have follow up?

There are no data concerning the benefit of follow up in patients with AKs. Patients and their carers should be educated regarding changes that suggest malignancy. Those at high risk of nonmelanoma skin cancer, e.g. organ transplant recipients, may warrant follow up; the presence of numerous AKs is an indicator of this risk.

Are there high-risk groups and is their management different?

Patients with multiple and confluent AKs are likely to be at higher risk of nonmelanoma skin cancer, particularly patients with organ transplants who are estimated to have 50–100 times the risk of an age- and sex-matched control population.[56,57] Anecdotal and limited trial data suggest that treatments for AKs in transplant patients are less effective than in the general population,[58] perhaps because AKs are more proliferative and hyperkeratotic in this group, or because new lesions rapidly appear in the treated site. One study in transplant recipients failed to demonstrate a reduction in the development of subsequent skin cancers in those areas of skin previously treated for AKs with PDT.[57]

Cost-benefit of treatment

Most AKs result in few or no symptoms and are not dangerous. Where there is a wide range of treatments it is necessary to balance the benefits of treatment against side-effects. In many health care systems this calculation will have some element of cost-benefit, where the cost is to the state and the indication must justify the expense. These guidelines are not able to give details on the complex matter of cost-benefit, but it is apparent that some treatments are considerably more expensive than others. Where outcomes are comparable and morbidity of treatment tolerable, we have tended to give a higher strength of recommendation to the cheaper treatment or one that is more easily used in primary care.

Summary of recommendations

AKs represent a spectrum of clinical complaint and pathology. Most patients can be diagnosed and managed in primary care. In many instances, management may entail little or no medical treatment other than advice on sun avoidance and self-monitoring. Where there is clinical concern or the patient specifically wants treatment, cryosurgery or one of the many topical therapies can be employed taking into consideration the specifics of the situation. If there is diagnostic concern or failure to respond to first-line treatment, a histological specimen, such as obtained at curettage with cautery or formal excision, may be both diagnostic and curative. Where AKs are multiple or confluent, at sites of poor healing or with poor response to standard therapies, PDT may be helpful. Such patients may also warrant long-term follow up for the associated increased risk of nonmelanoma skin cancer.

Audit points

AKs are a biological marker of sun damage and hence patients with AKs are at a greater risk of skin cancer than those with no AKs. Patients with AKs need to be educated on self-monitoring and the need to seek a medical opinion if they detect new lesions or changes in old lesions on their skin.

- Evidence that the patient was provided with information about AKs and sun damage
- Evidence that the patient is adequately informed concerning the nature of any treatment when given
- Evidence that the GP is provided with advice concerning how to evaluate and manage further AKs when they develop

• Evidence that high-risk patients and their GPs are aware of their status. This includes organ transplant recipients, those with multiple large AKs or previous SCCs. Such patients need a low threshold of referral for lesions of an actinic nature or unclear diagnosis.

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Appendix 1

Strength of recommendations and quality of evidence[a]

Strength of recommendations	
A	There is good evidence to support the use of the procedure
B	There is fair evidence to support the use of the procedure
C	There is poor evidence to support the use of the procedure
D	There is fair evidence to support the rejection of the use of the procedure
E	There is good evidence to support the rejection of the use of the procedure
Quality of evidence	
I	Evidence obtained from at least one properly designed, randomized controlled trial
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group
II-iii	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
IV	Evidence inadequate owing to problems of methodology (e.g. sample size, or length of comprehensiveness of follow up, or conflicts in evidence)

[a]A new system of evidence grading and recommendations has been adopted for new guidelines,[59] but these were introduced after the inception of this guideline.