BJD
British Journal of Dermatology

# British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017

D. de Berker,[1] J.M. McGregor,[2] M.F. Mohd Mustapa,[3] L.S. Exton[3] and B.R. Hughes[4]

[1]Bristol Dermatology Centre, University Hospitals Bristol, Bristol BS2 8HW, U.K.
[2]Department of Dermatology, Barts Health NHS Trust, London E1 1BB, U.K.
[3]British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.
[4]Portsmouth Dermatology Centre, Portsmouth Hospitals NHS Trust, Portsmouth PO3 6AD, U.K.

**Correspondence**
David de Berker.
E-mail: guidelines@bad.org.uk

**Accepted for publication**
7 September 2016

**Funding sources**
None.

**Conflicts of interest**
None declared.

D. de B., J.M.M. and B.R.H. are members of the Guideline Development Group, with technical support from L.S.E. and M.F.M.M.

This is an updated guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines (T&G) Subcommittee. Members of the Clinical Standards Unit who have been involved are P.M. McHenry (Chairman T&G), K. Gibbon, D.A. Buckley, I. Nasr, C.E. Duarte Williamson, V.J. Swale, T.A. Leslie, E.C. Mallon, S. Wakelin, S. Ungureanu, R.Y.P. Hunasehally, M. Cork, G.A. Johnston, J. Natkunarajah, F.S. Worsnop, N. Chiang, J. Donnelly (British National Formulary), C. Saunders (British Dermatological Nursing Group), A.G. Brian (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist) and M.F. Mohd Mustapa (BAD Clinical Standards Manager).

Guidelines produced in 2007 by the British Association of Dermatologists; reviewed and updated, 2016.

DOI 10.1111/bjd.15107



## 1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of actinic keratosis (AK).

The document aims (i) to offer an appraisal of all relevant literature up to February 2016, focusing on any key developments; (ii) to address important, practical clinical questions relating to the primary guideline objective, including accurate diagnosis and suitable treatment; (iii) to provide guideline recommendations and, where appropriate, some health economic implications; and (iv) to discuss potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic (see Section 13.0), in addition to an updated patient information leaflet (PIL), available at the British Association of Dermatologists (BAD) website (http://www.bad.org.uk/for-the-public/patient-information-leaflets).

### 1.1 Exclusions

This guideline does not cover bowenoid AK or actinic cheilitis.

## 2.0 Stakeholder involvement and peer review

The Guideline Development Group (GDG) consisted of consultant dermatologists. The draft document was circulated to the BAD membership, the British Dermatological Nursing Group, the Primary Care Dermatological Society, the British Society for Skin Care in Immunosuppressed Individuals, and Age U.K. for comments. These comments were actively considered by the GDG, and peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

## 3.0 Methodology

This set of guidelines has been developed using the BAD recommended methodology,[1] with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument

(www.agreetrust.org).[2] Recommendations were developed for implementation in the National Health Service (NHS) using a process of considered judgement based on the evidence. The PubMed, MEDLINE and EMBASE databases were searched for meta-analyses, randomized and nonrandomized controlled clinical trials, case series, case reports and open studies involving AK published in the English language from January 2004 to February 2016; the search terms and strategies are detailed in Appendix S1 (see Supporting Information). Additional relevant references were also isolated from citations in the reviewed literature, as well as specific targeted searches for systemic treatments and AK developing into squamous cell carcinoma (SCC) as a result of specific new treatments.

All identified titles were screened, and those relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed by the GDG, with a third round of review and selection for photodynamic therapy (PDT) publications given their number and complexity. Disagreements in the final selections were resolved by discussion with the entire GDG. The full papers of relevant material were obtained. The structure of the 2007 guidelines was then discussed and re-evaluated, with headings and subheadings decided; different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the selected literature with discussions within the GDG to resolve any issues. All subsections were subsequently collated and edited to produce the final guideline.

## 4.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines, and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English-language references was a pragmatic decision, but the authors recognize this may exclude some important information published in other languages.

## 5.0 Plans for guideline revision

The proposed revision of this set of recommendations is scheduled for 2021; where necessary, important interim changes will be updated on the BAD website.

## 6.0 Background

Actinic keratoses (synonymous with 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 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 the lesion is known as SCC *in situ* (Bowen disease). 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.

Actinic keratoses are generally considered to be premalignant lesions with low individual potential for invasive malignancy and potential for spontaneous regression. AKs present as discrete, sometimes confluent, patches of erythema and scaling on predominantly sun-exposed skin, usually in middle-aged and elderly individuals. Clinically, they are graded on a three-point scale according to magnitude. Field change might include any or all of these lesions (Table 1).[3] At grade 1 the lesion is just visible and palpable (gritty to feel and difficult to see), grade 2 lesions are usually red and scaly (easily felt and seen), and grade 3 corresponds to thicker, hyperkeratotic lesions. Grade 3 AKs can be difficult to differentiate from small, early SCCs, which, if excised, may be reported to have early or equivocal invasion.

They are often asymptomatic but may occasionally be sore or itch; lesions may be single or multiple. When multiple, the concept of 'field change' is used to describe an area of skin that is involved extensively with actinic damage.[4] 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.

### 6.1 Aetiology

Actinic keratoses are the result of chronic exposure to ultraviolet (UV) radiation, predominantly on skin of the head and dorsa of the hands, in fair-skinned individuals.[5] In addition, UVB-specific p53 mutations have been demonstrated in AKs, providing molecular evidence in support of a role for sunlight.[6] There is a high prevalence of keratinocyte cancer, including AKs, in those receiving chronic immunosuppression, particularly organ transplant recipients,[7] but also patients on long-term treatment for inflammatory bowel and rheumatological disease, although this is not as well documented. Other possible risk factors include exposure to arsenic[8,9] and chronic sunbed use.[10–12]

**Table 1** Grades of actinic keratosis (AK)[3]

| | |
|---|---|
| Grade 1 | Mild; pink or grey marks with slight scale or gritty to touch |
| Grade 2 | Moderate; thicker hyperkeratosis and easily detected |
| Grade 3 | Severe; hypertrophic, thick keratin |
| Field change | Confluent areas of several centimetres or more with a range of features matching any or all of the grades of AK |

### 6.2 Incidence and prevalence

It is likely that the incidence of AKs is underestimated. It is difficult to measure the burden of AKs reliably in individuals and in populations.[13]

In prevalence studies in Galway, South Wales and Merseyside, 19–24% of individuals aged > 60 had at least one AK.[14–16] AKs were also present in 3·6% of men aged 40–49 years.[16] A linear increase in prevalence was found with age (from 60 to 80 years) in men but not in women in another U.K. study, and the rate of new AKs was estimated to be 149 per 1000 person-years.[15] Over 30% of those attending a dermatology clinic (mean age of attendance 61 years) in Austria had AK. By the age of 70 years, > 70% of those attending had AK, with the majority (70%) on the head and neck.[17] A Rotterdam prevalence study of > 2000 Dutch men and women, mean age 72 years, found AK in 49% of men and 28% of women.[18]

### 6.3 Natural history: spontaneous regression and malignant transformation

Patients with AK have a chronic disease. The presence of a single lesion is a marker of excessive sun exposure and is associated with the development of further lesions. Point-prevalence studies demonstrate that lesions regress and relapse over time (this is probably relevant in the case of grade 1 and 2 lesions). Figures range between 25% and 70% for apparent resolution of AKs over a period of 1–4 years.[15,19,20] Prospective evaluation demonstrates a low rate of malignant transformation, with less than one in 1000 AKs developing into SCC per annum.[21] In a US study, 0·6% of patients developed an SCC in the AK field within the first year – rising to 2·57% at 4 years.[20] The higher rate of apparent transformation in the US study probably reflects the higher risk status of this predominantly male veteran population.

Nonetheless, there is evidence that AKs are a marker of excess risk for nonmelanoma skin cancer (NMSC). Mathematical models derived from the study undertaken by Marks *et al.* predict that for an individual with an average of 7·7 AKs, the probability of developing an SCC within a 10-year period is approximately 10%.[22]

When 918 adults (mean age 61 years) with AKs but no previous history of skin cancer were followed prospectively for 5 years, the incidence rates for basal cell carcinoma (BCC) and SCC were estimated at 4106 and 3198 per 100 000 person-years, respectively, representing an excess risk compared with the general population.[23] A sixfold excess risk for NMSC or melanoma was found in a representative sample of the US Medicare population with AKs compared with those without ($P < 0{\cdot}001$).[24]

Despite the proximity of AKs and SCC when they occur on chronically sun-damaged skin, and the histological and molecular similarities between them,[25] debate continues concerning whether they are separate but similar pathologies developing in tandem or whether one leads directly to the other. In one prospective photographic monitoring study over 5 years, it appeared that 65% of SCCs arose at a site of previously documented AK.[20] A recent systematic review of 24 eligible studies examining the natural history of AKs concluded that there were no reliable estimates concerning the frequency of AKs developing into invasive carcinoma.[26]

In summary, combined data suggest the possibility of regression and a low risk of malignant progression for any given AK. The presence of AK (particularly in high-risk patients – see Section 7.6 – with multiple AKs or field change) predicts an excess risk for subsequently developing an NMSC or melanoma compared with a matched population.

### 6.4 Investigation and diagnosis

Diagnosis of AK may be made in primary or secondary care and as part of a general skin examination associated with assessment of sun damage, focal keratotic lesions or skin cancer. Teledermatology has been cited as an effective means of diagnosis.[27] Dermoscopy can be employed with a range of defined dermoscopic features.[28] People with chronic fluctuating disease may learn self-diagnosis but are advised to corroborate their assessment with a healthcare professional. Such models of patient-led monitoring and action are advocated in other chronic diseases such as diabetes mellitus,[29] where motivated self-management is a significant element in improved outcome.[30] Diagnosis is typically on clinical grounds. Uncertainty may arise in distinguishing AKs from superficial BCC, SCC *in situ*, invasive SCC and even amelanotic melanoma, where a skin biopsy or excision for histological examination may be indicated. Where invasive malignancy is in the differential, the patient care should be shared with a member of a skin cancer multidisciplinary team. At the diagnosis of AK, the location and thickness (e.g. grade 1, 2 or 3)[3] should be documented; location is best recorded on a diagram.

### 6.5 Should actinic keratoses be treated?

The natural history of individual lesions suggests that treatment is not universally required on the basis of preventing progression into SCC.[15] An indirect benefit of treatment is the demonstration of lesions not responding to normal therapy, which may represent a subgroup with higher malignant potential. There is a body of professional opinion that believes AKs are part of a spectrum that includes SCC *in situ*, and that prevention of SCC is therefore the reason for therapy.[31] A Cochrane review of treatment of AK did not find any evidence that treatment of AK resulted in reduction in presentation of invasive SCC.[32] There is inadequate evidence to justify treatment of all AKs to try to prevent malignant change.

The most appropriate management plan should be determined by the patient's preferences and clinical circumstances, which should take into account the extent, duration and presence of symptoms, severity of lesions and other associated risk factors for skin cancer, in addition to the patient's general health and well-being. A quality-of-life questionnaire (AKQoL)

has been established and validated.[33] In particular, patients express concern with respect to (i) the disease itself, (ii) side-effects and difficulties with treatment, (iii) association with the term cancer where AK is a risk factor for SCC, and (iv) the need to adjust sunshine behaviour on a background of long-acquired habits and preferences.[34]

## 7.0 Management

Many options are available for the treatment of AKs. The main patient-centred considerations are the symptoms and cosmetic burden of the AK, the efficacy and burden of treatment, and the threat of evolution of the AK into a more bulky lesion or invasive SCC. Healthcare professional considerations overlap with these, but include others such as efficacy, a flexible regimen, availability in primary and secondary care and cost. An additional aspect of management is consideration of the patient's overall risk of skin cancer and the wider skin examination. In the Rotterdam study on the prevalence of AK in the general population, participants with ≥ 10 AKs (13·6%) had a threefold higher risk for having a history of SCC compared with participants with four to nine (4·0%).[18] Full-body skin examination revealed a skin cancer (BCC, SCC or melanoma) in 4%. The correlation between skin cancer and number of AKs led the Dutch group to advocate shorter follow-up intervals and more active treatment in those with ≥ 10 AKs, while not defining an interval and acknowledging the resource implications for this 5% of the population.

At the outset of management, the location and grade (Table 1) of the AKs should be defined to enable monitoring, response to treatment or evolution. This can be done using drawings, body maps and photography, often with lesions numbered.

Management can be directed at individual lesions or over a wider area (Fig. 1). This distinction represents lesion vs. field treatment. Field-based treatment can act to manage a range of actinic changes in a zone such as the forehead, scalp or central face, and may provide some benefit in reduction of onset of new lesions.[35] Topical therapies, skin peels[36–39] and PDT are suitable. Usually, focal destructive therapies such as curettage and cautery or cryotherapy are limited to lesion treatment (Table 2).

A European AK guideline achieved consensus through a voting and weighting method with advice grouped according to the isolated, field-associated or skin-cancer-associated distribution of the AKs. There remained a preference for cryosurgery for isolated lesions and curettage for larger ones. Otherwise, preferences revolved largely around different strengths of the common main agents, namely 5-fluorouracil (5-FU), imiquimod, ingenol mebutate and variants of PDT. Diclofenac in hyaluronic acid and imiquimod at 2·5% were not favoured. In immunosuppressed patients there was a preference for the stronger formulations of all products. Laser was not considered a good choice for any circumstance other than treatment of field disease.[40]

### 7.1 No treatment (strength of recommendation A, quality of evidence 2++)

Summaries of the levels of evidence and strengths of recommendation are given in Appendices 1 and 2.

Any perspective on nontreatment should be based on a whole-patient assessment, risks, comorbidities and preferences. The fact that many AKs remit does not diminish the counterbalancing point that they are associated with UV exposure and the development of melanoma, SCC and BCC. All patients need clear information on this risk and their own risk of SCC in general so that, irrespective of the diagnosis of AK, they know to present early for assessment if a lesion bleeds, is painful, grows significantly or becomes protuberant. All patients should be advised regarding sun protection.

### 7.2 Primary care

Patients with AK will ask their general practitioner (GP) for diagnosis and treatment advice. Most AKs can be diagnosed and treated in primary care.[41] In healthcare systems with a primary-care physician as the first contact, skin monitoring of sun-exposed surfaces of the head and neck and dorsa of hands is possible on an opportunistic basis and can be coupled with relevant prevention and self-care advice.[42] Specialist dermatology nurses can play a similar role and are able to prescribe treatment in some healthcare systems.[43] The Primary Care Dermatology Society has developed guidance on the management of AK in primary care in the U.K.[44,45] Teledermatology has been used to support the diagnosis and management of AK in primary care with specialist guidance.[27] AKs are part of the spectrum of actinic damage, which, once present, is managed rather than cured.

**Consider referral for specialist care when:**

- AK fails to respond to standard treatments;
- multiple or relapsing AKs represent a management challenge;
- AK occurs in the long-term immunosuppressed;
- lesions are likely to be AK, but there is concern that they might be SCC (use the 2-week-wait route for possible skin cancer), for example when they are (i) bleeding, (ii) painful or (iii) thickened with substance when held between finger and thumb.

### 7.3 Secondary care

Secondary-care referral is required for diagnosis and/or management if the lesion might represent an invasive SCC.[41] All regions of the U.K. have dedicated 2-week-wait or 'urgent cancer' pathways. In addition, if treatment in primary care for AK is unsuccessful, then referral is warranted for management alone. This includes patients with extensive disease or who are immunosuppressed (see bullet points above).

Following diagnosis in secondary care, treatment can be initiated with a future management plan for continued patient

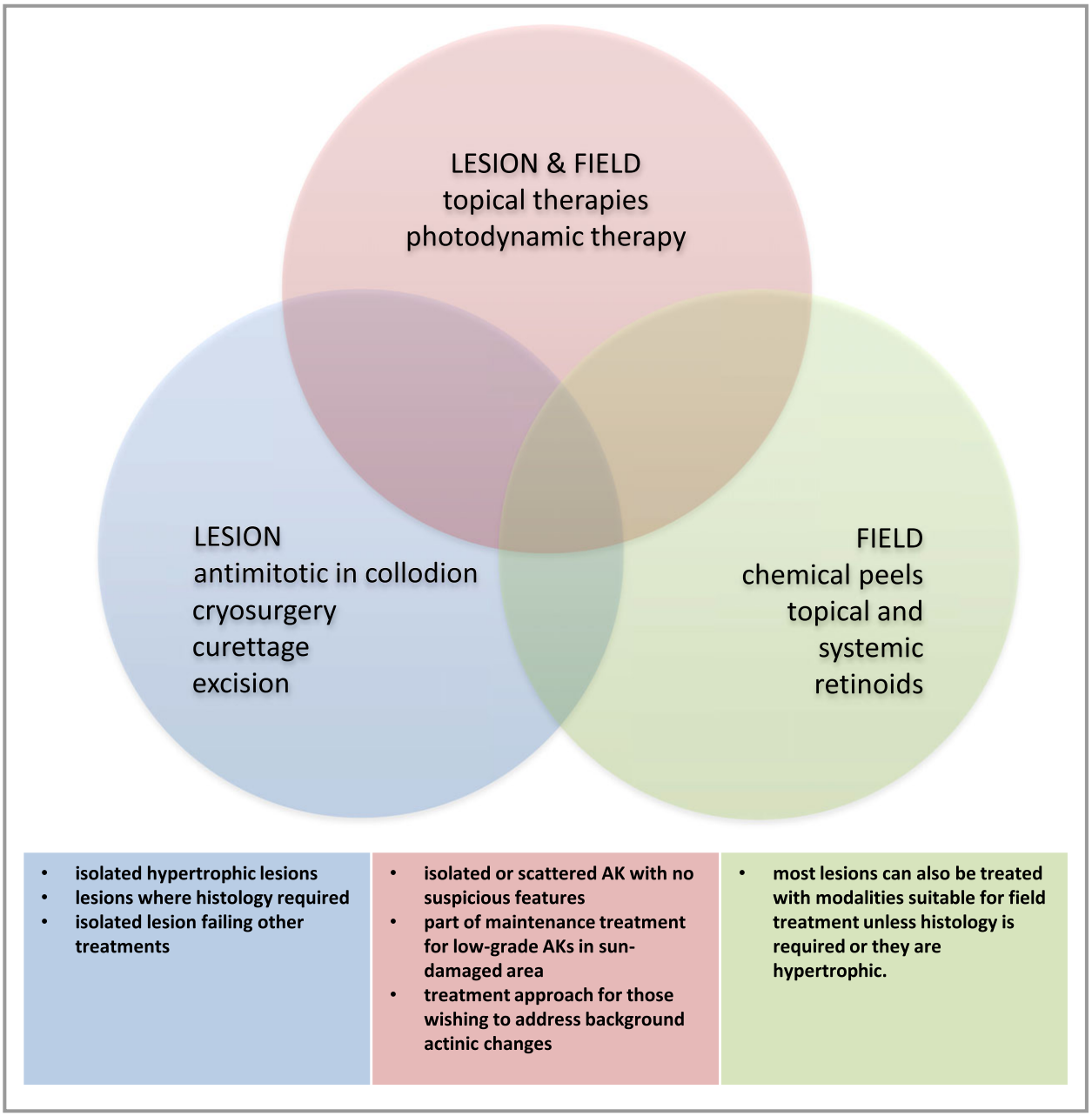


**Fig 1.** Venn diagram illustrating the overlapping nature of lesion- and field-based treatments for actinic keratosis (AK).

self-care (see Section 7.4) in collaboration with the GP. Histological diagnosis can be provided through a range of surgical procedures (see Sections 8.3 and 8.4) determined by lesion and circumstance. Follow-up in secondary care can be warranted to assess outcomes of treatment, extensive disease, patients with associated skin cancers, or those with other considerations such as immunosuppression. Nurse clinicians may contribute to the care pathway.

### 7.4 Self-care

Actinic keratosis is a chronic disease. Once patients have the diagnosis of AK, it is usually the start of a continued process of further lesions and relapse. They may also develop related pathology such as solar lentigo, lentigo simplex, SCC *in situ* and NMSC.

Patient education is important in enabling self-care, with early self-diagnosis, ongoing intermittent treatment and awareness of the risk of skin cancer and how to minimize this risk (see the AK PIL available at http://www.bad.org.uk/for-the-public/patient-information-leaflets). Most patients with mild AK will be seen in primary care and can manage their disease with topical therapy. Corroboration of diagnosis with the GP is advisable before treatment of new lesions. Short-term therapies (e.g. 4 weeks) may need renewal of prescription when expired to ensure maintained efficacy. An

 

**Table 2** Factors determining the choice of active therapy from nine main alternatives. The scoring is based on the authors' evaluation of efficacy, ease of use and morbidity

| Choice | 5-FU cream 5% | 5-FU cream 0·5% with salicylic acid 10% | Diclofenac gel 3% | Imiquimod 5% | Imiquimod 3·5% | Ingenol mebutate[a] | Cryosurgery | Curettage | MAL-PDT | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| Main characteristic of AKs | | | | | | | | | | |
| Single AKs (low number) | •••• | •••• | •• | •• | •• | •• | •••• | • | • | |
| Field change (high number) | •••• | •• | ••• | ••• | ••• | ••• | ••• | • | ••• | |
| Grade 1 or 2 (thin or medium) | •••• | •••• | ••• | ••• | •• | ••• | ••• | • | •• | Thin lesions may not always require treatment |
| Grade 3 (hypertrophic) | • | •• | • | • | • | • | •• | •••• | • | Histology may be required. Curettage or formal excision may be preferred |
| Isolated lesions failing to respond to other therapies | • | •• | • | • | • | • | •• | •••• | • | Histology may be required. Curettage or 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. See manufacturer's recommendations |
| Confluent scalp | •••• | ••• | ••• | •••• | ••• | ••• | ••• | • | •••• | Pretreatment with salicylic acid 5% ointment may improve outcome |

(continued)

**Table 2** (continued)

| Choice | 5-FU cream 5% | 5-FU cream 0·5% with salicylic acid 10% | Diclofenac gel 3% | Imiquimod 5% | Imiquimod 3·5% | Ingenol mebutate[a] | Cryosurgery | Curettage | MAL-PDT | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| 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 in some instances |
| Back of hands | •••• | •••• | •• | •• | •• | •• | •••• | ••• | ••• | Courses of topical therapy may need to be extended, and pretreatment with salicylic acid 5% ointment may improve outcome |
| Comments | Flexible with multiple treatments from one prescription. Good for self-directed care | Collodion base may enable more precise placement of treatment. Salicylic acid probably increases suitability for thickened lesions | Low-morbidity treatment suitable for thin AKs over a wide area | Variable response based on patient biology, with some instances of substantial side-effects | Possible slight reduction of side-effects with lower concentration | 2 or 3 days' application per treatment course makes it easy to remember, but reduces flexibility or ability for patient to modify according to side-effects | Reduces need for patient involvement, but increases dependency on medical provision of treatment; removes self-care and can cause scarring | Good for provision of histology and high efficacy for isolated thicker lesions. Not practical as routine treatment, leaves scars and requires local anaesthetic | Good treatment for areas of confluent disease and poor response to other treatments. Requires dedicated equipment and secondary-care provision in most instances | |

AK, actinic keratosis; FU, fluorouracil; MAL-PDT, methyl aminolaevulinate photodynamic therapy. •••• Good treatment; ••• fair treatment; •• can be used depending on circumstances; • rarely used in these circumstances. [a]Dosed at 150 μg $g^{-1}$ on the face and 500 μg $g^{-1}$ on the limbs and trunk.

important part of patient education is awareness of the side-effects of treatment before they start therapy. Many cause short-term redness, soreness and sometimes crusting or oozing. If this is not anticipated it can cause distress and abandonment of treatment, where a pause would have been more appropriate.

### 7.5 Prevention

There have been three randomized controlled trials (RCTs) (two in Australia and one in the U.S.A.) in patients > 50 years old, many of whom had a history of AKs, to show that sunscreen, used to prevent unintentional sun exposure, is associated with a small decrease in the incidence of SCCs and AKs (but not BCCs) over a short follow-up period.[46–48]

More active treatment with a 4-week course of 5-FU, 5% twice daily to a field of involved skin can reduce the rate of onset of new AKs in that area over the subsequent 18 months when compared with placebo.[35]

There are no studies to show that sun avoidance reduces the risk of development of AKs and skin cancer in a population without AKs. Nonetheless, it is reasonable to hope that the effect of public health campaigns over the last few decades will have an impact on this risk. Such practices may have a bearing on vitamin D levels, which warrant review in those patients subject to high levels of sun avoidance or who have other risk factors for diseases related to low vitamin D.[49]

### 7.6 High-risk cases

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

Patients with multiple and confluent AKs are likely to be at higher risk of NMSC than those with single lesions. Patients on chronic immunosuppressive therapy are at increased risk for skin cancer. Organ transplant recipients are reported as having 50–100 times the skin cancer risk of an age- and sex-matched control population.[50,51] It is recommended that high-risk patients have closer follow-up[52] and more rigorous treatment[40] for premalignant lesions, including SCC *in situ* and AK, together with a lower index of suspicion for skin biopsy to exclude malignancy. Nonetheless, there is no evidence that such measures reduce the risk of new skin cancers, although they may reduce morbidity from surgery and minimize the risk of recurrence.

Treatment for AKs in transplant patients may be less effective than in the general population.[53] Outcomes may be confounded by the large number of proliferative and hyperkeratotic lesions in this group. Studies have not found a reduction in subsequent skin cancers in areas previously treated for AKs with PDT.[51] Oral retinoids have been used to reduce the risk of SCC in transplant patients at high risk of getting skin cancer, but the effect on AKs is not reported.

A single study reported that capecitabine, used in 15 patients, reduced the risk of SCC,[54] BCC and AKs in organ transplant recipients, but toxicity is likely to limit its use.[55]

## 8.0 Treatment

Treatment needs to address a wide range of variables including the nature of the AK, the body site, patient preference, the premorbid state of the patient and previous treatments tried. Added to this is the large number of therapeutic agents, their modes of application and the flexibility with which each agent can be used. Given this backdrop, it is to be expected that there is variation in clinical practice. Table 2 attempts to bring a broad perspective to the options. In some instances it might be viewed in combination with Table 3, which is an approximation of a simplified cost–benefit analysis.

### 8.1 General

Lifestyle, dietary fat,[56] workplace and genetics are likely to make a difference to the risk of getting AK, mainly relating to the levels of UV radiation exposure.

#### 8.1.1 Emollient (strength of recommendation B, level of evidence 2+)

Elderly, sun-damaged skin is often dry, and emollient can be part of a management regimen. The direct effect of emollient on AKs is not clear. Additives such as urea or salicylic acid may provide benefit. There are no trials dedicated to the study of palliative therapy of AKs, but emollient or gel vehicle has been employed in the placebo arm of many trials. The vehicle limb of an RCT of diclofenac gel in hyaluronan vehicle described clearance of the target lesion in 44% of patients using the vehicle after 60 days.[57] Less dramatic results were seen with the cream vehicle used in trials of imiquimod applied two or three times a week for 4 weeks, reporting complete clearance of treated AKs in 0%,[58] 2·4%[59] and 14·1%,[60] with the latter treated three times a week for 8 weeks.

#### 8.1.2 Sun protection and sunscreen (strength of recommendation A, level of evidence 1++)

There is no specific information or evidence on sun protection other than through studies on sunscreen. Sunscreen has a combined emollient and photoprotective effect. A randomized, placebo-controlled trial of sunscreen with sun protection factor (SPF) 17 applied twice daily to the face for 7 months showed sunscreen to be more effective than emollient in terms of the total number of AKs and new lesions.[46] A single, daily application of sunscreen with SPF 16 in Queensland, Australia, also showed it to be more effective than discretionary use of the same sunscreen over a 2-year period in the reduction of AKs.[61] A similar approach in the same setting also reduced the incidence of cutaneous SCC.[48] A 24-month study of daily use of sunscreen (SPF > 50, high UVA absorption) in 120 case-controlled organ transplant recipients showed significant reduction in AKs and NMSCs arising during the study.[49]

**Table 3** Cost, efficacy, flexibility and setting of the main treatment options in AK. Data between treatment groups are not always based on similar sampling and outcome measures. The levels of evidence contributing to this table range from 1++ to 4

| | Period of evaluation (longer than active treatment) | Reduction in AKs based on [a]observational studies, [b]RCTs or [c]meta-analysis (values do not reflect excess over control) | Cost range per item | Dispensed item | Add-on cost of staff time or equipment. Primary care or [secondary care]. [d]Typically requires 2 visits | Flexible regimens | Amenable to patient-directed care and monitoring | Amenable to primary care |
|---|---|---|---|---|---|---|---|---|
| No treatment | Periodic, indefinite | Up to 21%[a,15] | ♦ | | 0 | • | • | ••• |
| Emollient or vehicle | Periodic, indefinite | 0–44%[b,57,60] | ♦ | | 0 | • | • | ••• |
| Sunscreen (UVA 3/ SPF 17–50) | Periodic, indefinite | 17–36%[b,46,47] | ♦ | 500 mL | ♦[♦♦] | • | • | ••• |
| 5-Fluorouracil 5% | 2–4 months | 70–78%[b,36,66] | ♦ | 40 g | ♦♦[♦♦♦♦][d] | ••• | •• | •• |
| Imiquimod 5% | 2–4 months | 50%[c] to 84%[b,74,75] | ♦/♦♦ | 12–24 sachets | ♦♦[♦♦♦♦][d] | ••• | •• | •• |
| Imiquimod 3·75% | 3–4 months | 34–36%[b,85] | ♦♦♦/♦♦♦♦ | 28–56 sachets | ♦♦[♦♦♦♦][d] | ••• | •• | •• |
| Diclofenac gel 3% | 2–4 months | 19–70%[b,57,90] | ♦/♦♦ | 50–100 g | ♦♦[♦♦♦♦][d] | •• | •• | ••• |
| Ingenol mebutate (150 μg $g^{-1}$ face, 500 μg $g^{-1}$ limbs and trunk) | 1–2 months | 34–42%[b,92,93] | ♦♦ | 2–3 single-application 0·47-g tubes | ♦♦[♦♦♦♦][d] | • | ❍ | •• |
| MAL-PDT | 1–2 months | 69–93%[b,107,119,127,176] | ♦♦♦ | Single treatment tube | £427–£928[177] | •• | ❍ | ❍ |
| Cryosurgery | 1–2 months | 39–88%[a,103,106] | Not known | Not applicable | ♦♦[♦♦♦♦][d] | •• | ❍ | • |
| Combination therapies | | | | | | | | |
| 5-Fluorouracil 0·5% and salicylic acid 10% | 2–4 months | 55%[a] to 77%[b,71,72] | ♦ | 25 mL | ♦[♦♦] | •• | •• | ••• |
| Diclofenac gel and cryosurgery | 2–4 months | 46–100%[a,156,157] | ♦/♦♦ | 50–100 g | ♦[♦♦] | •• | • | • |
| Imiquimod and cryosurgery | 2–4 months | 59·5%[a,86] | ♦/♦♦ | 12–24 sachets | ♦♦[♦♦♦♦][d] | •• | • | • |
| Imiquimod and MAL-PDT | 2–4 months | 89%[a,160] | ♦/♦♦ | 12–24 sachets plus single treatment tube | ♦♦[♦♦♦♦][d] plus £427–£928 | •• | • | ❍ |
| Comments | | | Standard package size or course of treatment: BNF 2014, edition 66 | | Costs drawn from NHS publications | | | |

AK, actinic keratosis; BNF, British National Formulary; NHS, National Health Service; MAL-PDT, methyl aminolaevulinate photodynamic therapy; RCT, randomized controlled trial; SPF, sun protection factor; UVA, ultraviolet A. Cost key: ♦ £0–50; ♦♦ £51–100; ♦♦♦ £101–150; ♦♦♦♦ £150–200. Care key: ❍ not amenable or flexible; • some flexibility/amenability; •• moderate flexibility/amenability; ••• very flexible/amenable. First hospital clinic attendance NHS tariff 2014–15: £104.[178] Hospital follow-up attendance: £68. GP visit: £44.[179]

### 8.2 Active treatments

All topical therapies for AK may result in side-effects of irritation. Some AKs proceed to ooze, crusting and soreness with local swelling. Details are cited in this guideline for the individual treatments and are included in the relevant PILs. It is important that the patient understands the extent of the area to be treated and anticipates the side-effects. The size of area will depend on a range of factors including the therapy, focal or scattered pathology and the conceptual model (field- or lesion-based treatment). Where morbidity is an ascendant concern, treatment should be initiated over a small area such as 4–10 $cm^2$ with flexible frequency to establish tolerance and confidence. Some treatments define a ceiling of surface area based on the aliquot of prescribed item, for example one tube of ingenol mebutate is a single dose for 25 $cm^2$. Imiquimod 5% is issued in 250-mg sachets where directions include 'one sachet only' and to 'cover the area' typically with a centimetre margin around any pathology. Others recommend a maximum based on toxicity, such as 500 $cm^2$ for 5-FU 5%.

Patients should be provided with advice on how to manage side-effects, with strategies including a break in treatment, altering the frequency of application, use of emollient and in some instances application of topical steroid.

#### 8.2.1 5-Fluorouracil (strength of recommendation A, level of evidence 1++)

The majority of the data on topical therapies relate to the 5% concentration of 5-FU cream. 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.[62] It is a widely used, flexible and low-cost treatment.[63] It can be used either as lesional treatment or as part of field treatment. The side-effects with the latter can be substantial, and it is important that the patient is counselled about them, including soreness, redness and possible crusting. All of these can be minimized through reduction in the frequency of application or short breaks in a course of therapy. It is permitted to wash the area and apply thin emollient. If the reaction is excessive, weak steroid can be applied. It is important that the patient is enabled to learn how to use the treatment, as it is one they may require intermittently in the future and a bad initial experience can limit further use.

Many regimens cite twice-daily application over 4 weeks, but less frequent initial use may enable titration of the frequency of application against reaction, tolerance and efficacy. Use at poor healing sites such as the lower leg should always be undertaken with caution and may need supervision. More recently, 5-FU 0·5% in 10% salicylic acid has been evaluated and can be prescribed.[64] A wide range of open trials, dose-ranging studies and manipulations of the vehicle have been reported over the last 45 years, as well as two RCTs, confirming efficacy. A large, placebo-controlled RCT showed 5-FU 5% to be more effective than placebo in AK clearance and the reduction of follow-up cryosurgery treatments at 6 months.[35] A Cochrane review with subsequent meta-analysis of complete clearance results ranked the efficacy of all of the main treatments and put 5-FU at the top.[65]

Nine of the trials were controlled; 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 the trials. The minimum follow-up was $\geq 12$ months 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.[36,66] Kurwa *et al.* examined the lesional area of AKs on the back of the hands before and after treatment with 5-FU 5% cream twice daily for 3 weeks in a randomized right–left comparison with a single treatment with PDT.[66] 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,[67] but is adequate for those on the face.[36]

Witheiler *et al.* used 5-FU 5% cream on the face as the 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 trichloroacetic acid (TCA) 35% peel.[36] 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.[68] Six patients were followed for 9 months and showed an 86% clearance rate that was maintained. Epstein followed this study with a similar protocol and sample size, except that evaluation was done by dermatologists given a series of photographs and blinded to the sequence.[69] Eight of 13 patients failed to show any improvement, with the conclusion that pulsing 5-FU over a period $< 10$ weeks is not effective. A comparison of use twice daily for 3 weeks against twice daily for 1 day a week for 12 weeks showed the infrequent regimen to be 80% as effective when evaluated at the final assessment at 52 weeks.[70]

The mixed quality and size of these studies mean it is difficult to provide a firm interpretation, but the indication is that pulsed therapy may work for some patients and enable more protracted therapy with reduced morbidity. Such an approach can be useful for sensitive areas or people reluctant to use treatments that provoke redness and crusting. However, for some people it may fail to show benefit, and increased

frequency of use or an alternative treatment may need to be employed.

5-FU 0·5% in 10% salicylic acid has been assessed, where salicylic acid may be acting as a keratolytic to enhance the efficacy of 5-FU. In the initial open trial, statistics were undertaken per AK rather than per patient.[71] In this framework, it is not possible to report the complete cure of any single patient. However, the clinical clearance rate for individual AKs was 77%, with no control or blinding. Subsequent evaluation against salicylic acid vehicle and diclofenac 3% in hyaluronic gel has been undertaken.[64] Daily application with a brush for 6–12 weeks or the point of clearance was compared with twice-daily diclofenac gel over the same period. Eight weeks post-treatment, complete clearance was determined to be achieved in 55·4%, 32% and 15·1% of the patients using the study product, diclofenac and vehicle, respectively; the AKs were grades 1 and 2. A follow-up phase of the same study measured the rate of relapse of individual lesions rather than relapse from complete clearance.[72] With this measure, the rate of relapse measured per lesion was less at 12 months with 5-FU 0·5% in 10% salicylic acid (14·2%) than diclofenac 3% gel (19%) ($P = 0·02\%$).[72] The nature of the application makes it suitable for lesion-directed therapy rather than field therapy. The license highlights the benefit of the salicylic acid vehicle as a means of addressing more keratotic AKs. About 50% of patients discontinue treatment at 6 weeks due to disappearance of the AK.[73]

### 8.2.2 Imiquimod 5% cream (strength of recommendation A, level of evidence 1++)

Imiquimod is a topical immune-response modifier. It is available as a 5% and a 3·75% cream. Most of the data on treatment response pertain to the 5% cream and are considered first. In the U.K. it is licensed for use in clinically typical, nonhyperkeratotic, nonhypertrophic AKs on the face or scalp in immunocompetent adults, when the size or number of lesions limits the efficacy and/or acceptability of cryotherapy, and other topical treatment options are contraindicated or less appropriate. It is applied at night and washed off in the morning 8 h later. Courses are three times a week for 4 weeks, which can be repeated for a further 4 weeks if needed.

A meta-analysis of the use of imiquimod 5% cream from five RCTs using it two or three times a week for 12–16 weeks demonstrated a 50% complete clearance rate. This is similar to more brief and flexible regimens as per the license.[74] A small RCT against vehicle placebo showed clearance rates of 84% when used up to three times per week for 12 weeks.[75] Two RCTs with regimens of three times per week for 16 weeks and follow-up 8 weeks later gave 47% of subjects with complete clearance (vs. 7·2% with placebo)[76] and 57·1% (vs. 2·2% for placebo).[59]

A head-to-head open trial between imiquimod 5% (twice per week for 16 weeks), its cream vehicle and diclofenac 3% gel (twice daily for 90 days) showed complete clearance of 19·1%, 0% and 20% at the end of the respective treatment periods. After a further 24 weeks, these figures changed to 45%, 0% and 14·3%, respectively, illustrating that improvement continues to progress after the conclusion of imiquimod, in contrast to other treatments.[58] Similar results were reported for imiquimod 5% used three times a week for 4 weeks in 126 patients, and repeated for a further 4 weeks a month later in 79 of them and compared with cream vehicle. The global complete response in the combined groups was 55%, compared with 2·3% for vehicle, illustrating that personal variation makes it possible to tailor the duration of the regimen to the individual.[77] An RCT comparing imiquimod 5% cream on the face [three times a week for 4 (40%) or 8 (60%) weeks depending on response] with liquid nitrogen spray (10-s freeze to commencement of thawing) favoured liquid nitrogen, with complete clearance in 88% vs. 66·9%. However, the cryosurgery resulted in a higher number of pigmentary changes.[78]

The side-effects of imiquimod are similar to those of 5-FU, with severe erythema (30·6%), scabbing and crusting (29·9%) and erosions or ulceration (10·2%). Flu-like symptoms can also arise and are more likely if multiple sachets are used at each treatment or if it is being used for superficial BCC with more frequent applications than is typically the case for AK.[59] An instance of post-treatment eruptive keratoacanthomas has been reported.[79] 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. Side-effects are generally well tolerated, but it is important to counsel the patient carefully in order to anticipate those who have more extreme clinical reactions.[80]

There are limited long-term data on relapse after treatment, but in a three-armed RCT between cryosurgery, 5-FU 5% and imiquimod, the proportions of the intention-to-treat population maintaining clearance at 12 months were 1%, 33% and 76%, respectively.[81] The cryosurgery treatments were 20–40 s in duration, which is a dose at which scarring might be expected. This observation poses questions about this limb of the study. In an observational, 16-month follow-up study, 75·3% of those receiving treatment three times a week over 8 weeks were clear at 16 months, in comparison with 57·4% receiving the same treatment twice a week.[82]

There is a small number of studies on imiquimod 3·75% cream (strength of recommendation B, level of evidence 1+), which is licensed for treatment of AKs of the head and scalp with application once daily for two, 2-week periods separated by 2 weeks. Early studies had longer courses, applied once daily for two periods of 3 weeks separated by 3 weeks, over a 9-week course. Comparison with placebo vehicle 8 weeks after conclusion of treatment showed complete clearance rates of 5·5% (placebo) and 34%.[83] Where AKs responded they recurred in 60% of patients within 14 months.[84] Where treatment was given as per the licence at weeks 1 and 2, then 5 and 6, complete clearance was seen in 6·3% and 35·6% for emollient and imiquimod, respectively.[85] Where the

 

comparator was cryosurgery and emollient vehicle, imiquimod 3·75% following cryosurgery resulted in complete clearance in 59·5% of patients.[86]

Imiquimod 3·75% has also been used following cryosurgery as a supplementary treatment, improving the result of treatment of hypertrophic AKs on the forearm and dorsa of the hands over cryosurgery alone.[87] It is possible that the adverse side-effects associated with imiquimod 5% cream are less with the 3·75% formulation, and this might enable more field-based treatment over lesion therapy and improve patient tolerance.

### 8.2.3 Diclofenac gel (strength of recommendation A, level of evidence 1+)

Diclofenac 3% in a 2·5% hyaluronic gel is licensed for application twice daily for 60–90 days and can be applied as a lesion- or field-based treatment. Its mechanism of action for AK is not known, but may be related to inhibition of the cyclooxygenase pathway leading to reduced prostaglandin E2 synthesis. Diclofenac gel usually causes less intense local skin reaction than 5-FU or imiquimod 5% cream.[88] The reduction of side-effects is matched by reduced efficacy where diclofenac gel and 5-FU 5% are compared, but both achieve high levels (73% vs. 77%) of patient satisfaction.[89]

There are three vehicle-controlled studies in the treatment of mild AKs. In the first, patients were treated for a mean of 60 days, with a clearance of 70% of target lesions in the treatment group compared with 44% in those using the vehicle.[57] In the second study, treatment was for 90 days; 50% achieved complete clearance vs. 20% of those treated with vehicle alone ($P < 0{\cdot}001$).[90] In a three-armed RCT comparing diclofenac 3%, imiquimod 5% cream and base cream, the rates of complete clearance at the end of treatment were 19·1%, 20% and 0%.

In summary, these three different studies with diclofenac gel show 26%, 30% and 19·1% benefit over vehicle gel or base cream, respectively.[58] Extending treatment from 90 to 180 days gave an additional 5% complete clearance without a significant change in adverse effects.[91] Follow-up assessment was limited to 30 days post-treatment in the first two studies. In the third, clearance dropped to 14·3% at 24 weeks' follow-up. Diclofenac 3% gel used as part of a three-armed study with 5-FU 0·5% in 10% salicylic acid and vehicle resulted in a 32% rate (17% over vehicle)[64] of complete clearance, and a relapse rate of 19% at 12 months.[72] These data indicate moderate efficacy with low morbidity in mild AKs. Treatment was well tolerated and reported side-effects were mainly pruritus (41% estimated after 30 days' treatment) and rash (40% estimated after 60 days).[57]

### 8.2.4 Ingenol mebutate cream (150 μg $g^{-1}$ face and scalp, 500 μg $g^{-1}$ limbs and trunk) (strength of recommendation A, level of evidence 1+)

Ingenol mebutate is a diterpene ester extracted from the plant *Euphorbia peplus*. At a cellular level it appears to work through the disruption of mitochondrial membranes resulting in damage and death of host cells and promotion of cell-specific antibodies with consequent antibody-dependent, cell-medicated cellular cytotoxicity. It is licensed for the treatment of nonkeratotic, nonhypertrophic AK in adults (grade 1 and 2). It is sold in two strengths (150 and 500 μg $g^{-1}$), with the weaker one applied 3 days in succession to the chosen area on the face and scalp and the stronger one applied 2 days in succession to other sites. Each application is dispensed as a single tube of cream (three tubes for the face and scalp or two tubes for other sites) with scope to cover a field 5 × 5 cm. Use of the 150-μg $g^{-1}$ preparation on the face and scalp over 3 days resulted in a complete cure rate of 40% vs. 11·7% for vehicle 60 days after starting the treatment in one RCT,[92] and 42·2% vs. 3·7% for vehicle in another of similar size.[93]

Pooled data from two trials of this treatment regimen followed successfully treated patients for 12 months. There was relapse on the head and neck in just over half of the patients in the following year.[94] If residual lesions are re-treated at 8 weeks, clearance at 12 months increases from 27% to 50%.[95] Clearance on other body sites is less, at 34·1% vs. 4·7% for vehicle after application of the 500-μg $g^{-1}$ cream on two consecutive days, with relapse in just over half of the patients at 12 months. Specific sites such as the back of the hand are less likely to clear completely, with 18·5% vs. 0% for placebo.[96]

Side-effects peak at 4 days, which is after completion of the application of treatment. Common effects are redness, scabbing, pain and pustules, with most side-effects settling within 28 days.[93,94]

A 2015 update from the US Food and Drug Administration highlights the risks of severe adverse reactions, with local and systemic allergic features and herpes zoster infection. Within the update they emphasize the need 'to avoid applying the gel in, near, and around the mouth, lips and eye area'.[97] Extending the area of treatment of ingenol mebutate to 100 $cm^2$ resulted in no increase in treatment-related adverse events compared with 25 $cm^2$.[98] Clobetasol propionate, used twice daily for 4 days post-treatment, did not alleviate the symptoms or efficacy of ingenol mebutate.[99] This may be relevant to other treatments causing soreness.

### 8.2.5 Topical retinoids (strength of recommendation B, level of evidence 1+)

A range of older trials demonstrate a modest benefit with the use of topical retinoids in AK.[100] They may lend some additional benefit with respect to improvement in lentigines and reduced wrinkles. Their use is usually sustained rather than based on a limited course of treatment. Products include adapalene 0·3%, tretinoin 0·1% and 0·05% and topical isotretinoin 0·1%. Where adapalene 0·1% was compared with 0·3%, the latter was significantly more efficacious in achieving AK count reduction after 9 months.[101] Currently, tretinoin and isotretinoin are prescribable in the U.K. only in 0·025% and 0·05% concentrations, respectively, as topical antibiotic

combinations licensed for use in acne. A Veterans Association RCT exploring topical retinoid for chemoprevention of skin cancer was stopped early because of excessive all-cause mortality in the treatment group at interim analysis.[102]

**Key recommendations: topical therapies**

- Emollient and sunscreen with advice on sun protection might be a satisfactory treatment for people with fluctuating grade 1 AKs.
- Education at the outset of using active topical therapies is important to ensure a full understanding of how to apply treatment and the nature of the side-effects, which can be marked.
- Active topical therapy is suited to use in primary and secondary care. Where possible, a management plan should be formulated that enables the patient to be managed in primary care.
- Topical therapy is suited to use as lesion- and field-based treatment. Where used for field treatment, the size of the field needs to be defined with the patient to ensure anticipation and tolerance of side-effects.
- Failure of an individual lesion to respond to topical therapy indicates a need for further evaluation. This may include referral from primary care to secondary care or surgery to obtain histology and extend treatment.

### 8.3 Cryosurgery (strength of recommendation A, level of evidence 1++)

Cryosurgery is a long-established treatment for AKs requiring a cryospray (or cotton wool and orange sticks) and a supply of liquid nitrogen. Complete clearance rates vary according to the duration of freeze and the number of treatments, usually separated by 6–12 weeks. The relationship between duration of freeze and clearance was examined in a three-dose study with 12-month follow-up after cryosurgery. A duration < 5 s showed 39% cure, 5–20 s, 69% cure and > 20 s, 83% cure on the scalp and face.[103] Many more recent studies are based on head-to-head trials with PDT. 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.[104] 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.[105]

A more recent head-to-head study with methyl aminolaevulinate (MAL)-PDT employed cryosurgery (1 × 10-s freeze) as needed every 3 months for up to four visits with assessment at 12 months. It reported a complete response rate of 85%, with 77% needing only one treatment. Side-effects of cryosurgery of soreness, blistering, pigmentary change and scarring contributed to an overall patient preference for PDT.[78] In another study, a double freeze–thaw cycle given just once with no defined duration provided a complete clearance rate of 88% as judged at 24 weeks.[106] In a right–left, split-face study comparing MAL-PDT with a cryosurgery double freeze–thaw cycle retreated at 12 weeks as needed, MAL-PDT showed 89·1% cured lesions vs. 86·1% for cryosurgery, with no significant difference between them. Patient and clinician assessment of cosmetic outcome were in favour of MAL-PDT.[107]

Extensive cryosurgery over large areas has been referred to as cryopeeling, and can be used to treat fields of AKs and background damage.[108] 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.[109] The pretreatment of AK with 5-FU 0·5% for 1 week, prior to treatment of the remaining lesions with cryosurgery at the 1-month follow-up, may decrease the AK count at 6 months when compared with cryosurgery and vehicle pretreatment (reduced to 33% vs. 55%, $P = 0{\cdot}01$).[110]

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 the short- and long-term side-effects. In particular, patients should be aware of blistering, oedema, crusting and soreness. Doses appropriate for AK are usually < 10 s, but still carry some risk of damage to underlying structures such as tendons and nerves if applied on the back of the hands. Below the knee, slow healing can be a problem, particularly in the older patient group presenting with AK.

### 8.4 Surgery

There are no trials of surgery 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. Histological information can be useful in management of AK. It is unlikely that this would be a first-line treatment unless there was diagnostic uncertainty. Surgery addresses a focal lesion, and where AK presents in a field of actinic damage, it does not address this. 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 where SCC is a differential diagnosis, 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 still likely to represent adequate treatment. Exceptions would be where the size, histological type or location of an SCC would make curettage an unacceptable treatment.[111]

### 8.5 Systemic therapy (strength of recommendation C, level of evidence 2+)

Systemic retinoids have been assessed for their potential role in suppression or treatment of multiple AKs. Early studies employing etretinate showed the efficacy of this drug in

 

double-blind, crossover trials.[112] Anecdotal evidence over the last 20 years suggests that there can be some considerable morbidity in employing this treatment. In addition, there may be a rebound effect once the systemic therapy is stopped. However, these effects were not observed at the 4-month follow-up in the one available report on this subject.[113]

Use of systemic retinoids 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] Renal transplant patients given oral acitretin 0·4 mg $kg^{-1}$ showed some immunohistochemical normalization of keratin expression patterns, but a residue of histological dysplasia suggests potential for relapse when the drug is stopped.[114] Low-dose acitretin is currently given as a treatment option in the 'European best practice guidelines' for renal transplant patients with multiple dysplastic skin lesions.[115]

An international survey of 28 dermatologists managing skin disease in organ transplant recipients looked at the use of systemic retinoid.[116] In the setting of AK alone, only where the AK was extensive did the majority (56%) advocate systemic retinoid. Once patients start getting multiple (more than five) SCCs in addition to AK, the rate of prescribing increased to between 74% and 81% depending on whether the SCCs were high risk. Acitretin was the most common drug, at a starting dose of 10 mg (42%) or 25 mg (58%); 12% of respondents used isotretinoin.

There is little literature on the use of systemic cytotoxic agents in the immunosuppressed, mainly for the treatment of SCC but in the setting of extensive AK. Capecitabine given to 15 organ transplant recipients with frequent SCC, BCC and AK showed reductions in monthly incidence to 22%, 33% and 45% of pretreatment levels, respectively.[55] Side-effects resulted in 33% of patients stopping after 1 year.

The cyclooxygenase-2 inhibitor, celecoxib, taken for 9 months can reduce the number of BCCs and SCCs over an 11-month period, but does not appear to alter the number of AKs.[117] Overall, it may have a role in high-risk patients with multiple NMSCs, but it does not have evidence of a role for AK.[118]

### 8.6 Photodynamic therapy (strength of recommendation A, level of evidence 1+)

Photodynamic therapy combines a dedicated light source of appropriate wavelengths with the application of a photosensitizing cream to produce apoptosis and necrosis of the target tissue. Photosensitizing agents include 5-aminolaevulinic acid (5-ALA) and the methyl ester of 5-ALA, 5-MAL. BF-200ALA was recently used, showing increased stability and penetration.[119,120]

A range of light sources can be used.[121] Red narrow-spectrum light sources permit shorter illumination times and appear to give higher response rates.[119,120] Current knowledge of photosensitizers and light sources are detailed in the 2013 European Guidelines for PDT.[121] In most situations superficial crust or keratin is first removed with light curettage and photosensitizing cream, then the agent is applied under occlusion for 3 h prior to irradiation. Surface fluorescence with a Wood's lamp can help delineate lesions and identify persistent disease. Treatment can be painful but can be managed with cold-air analgesia or nerve blocks.[121,122] Erythema and crusting often occur but can be reduced by the use of plaster or physical sunscreens.[123]

Four studies report PDT to be more effective than placebo.[105,107,124,125] Three were randomized and one double blinded, with 80–211 subjects. Efficacy rates appear better for the face and scalp than the forearm and hands,[126] but there are no studies comparing the two sites. Response rates in the face and scalp range from 69% to 93%. Follow-up reported up to 24% recurrence at 12 months in an open-label study.[127]

There may be an increased response of PDT with fractionated light[128] and pretreatment with laser.[129] Both claimed better responses, but patient numbers were small and the side-effects greater with laser pretreatment. In a side-to-side comparative study of PDT vs. $CO_2$ laser treatment they were of equal efficacy but patient preference was for PDT.[130]

Three open-label RCTs compared MAL-PDT with cryosurgery. Two freeze–thaw cycles were comparable in one study[104] and inferior in terms of relapse in another.[107] A single cycle was inferior in the third study.[105] The efficacy of PDT was confirmed in a meta-analysis in 2014.[131] PDT has also been compared side to side in trials with 5-FU.[66] A right–left comparison of AK treatment on the backs of the hands showed a similar response for PDT and 5-FU, clearing lesions in 73% and 70% of cases, respectively. Three studies showed no difference between PDT and imiquimod.[132–134]

In a randomized study of 30 patients given up to two treatments with ALA-PDT or one to two courses of imiquimod (three times a week for 4 weeks), equivalent responses were seen 6 months after completion of treatment (65% vs. 55%).[134] PDT was more effective for grade 2 lesions.

A thin, self-adhesive patch has been developed for self-application.[135,136] In a multicentre RCT involving 449 patients, efficacy with active treatment was 82% after 12 weeks compared with 19% for placebo and 77% for cryosurgery. It is advocated as allowing self-application and avoiding the need for pretreatment curettage.

Daylight PDT involves the application of MAL to the skin without occlusion and subsequent exposure to ambient daylight. A high-SPF sunscreen without mineral filters is applied 15 min before the photosensitizing cream. Thirty minutes later the patient spends 2 h outdoors.

Five RCTs in Europe and Australia have confirmed the efficacy of daylight PDT compared with conventional PDT.[137–141] This was in mild (grade 1) to moderate (grade 2) lesions on the face and scalp. Clearance rates of 70–89% were reported. In European studies daylight PDT can be performed in all weather conditions,[141] but temperatures > 10 °C are advised for patient comfort. Consensus guidelines have also been produced.[142–144]

One comparative study was a right–left comparison of PDT with ingenol mebutate in grade 1 and 2 lesions (27 patients).

In both there was a 40% complete response rate, but PDT was better tolerated.[145]

### 8.7 Laser therapy (strength of recommendation B, level of evidence 1+)

In principal, dermabrasion, chemical peels and laser treatment should treat AKs, as skin is destroyed to a controlled depth. The majority of studies treat field change as well as individual lesions. These physical therapies come with significant risk of long-term side-effects including hypopigmentation and persistent erythema and scarring. The risk of such problems is greater with ablative rather than nonablative laser techniques, which also require anti-infective prophylaxis.[146]

There are no studies comparing laser treatment with no treatment or placebo.

A good-quality, prospective, randomized study of 5-FU (twice daily for 4 weeks) vs. erbium-doped yttrium aluminium garnet (Er:YAG) laser in 55 patients demonstrated significantly fewer recurrences in the laser group at 6 and 12 months, but more erythema and hypopigmentation in the long term. No data were reported on clearance at completion of treatment.[147]

A second prospective randomized trial of $CO_2$ laser vs. TCA 30% vs. 5-FU (twice daily for 3 weeks) with small patient numbers showed a significant clearance of lesions with all interventions at 3 months. The authors also claimed a delayed time to recurrence of NMSC compared with controls, but the controls were the dropouts from the study.[148]

Three retrospective case studies of $CO_2$ with or without Er:YAG lasers show clearance and reduced AKs at follow-up.[149] Two of these studies demonstrate 80% and 87% clearance at 12 months.[150,151] A split-face study of ablative, fractionated (i.e. multiple pinpoint treatments) $CO_2$ laser treatment demonstrated only a short-term reduction in the number of AKs, not sustained over 3 months.[152] One pilot study of nonablative fractional laser in 10 patients reported 46% clearance at 6 months and claimed minimal acute and long-term side-effects.[153]

Dermabrasion in open studies clears AKs on the face and scalp. Coleman *et al.* treated 23 patients, 96% of whom were clear at 6 months and 54% at 5 years.[154] Winton and Salasche treated five patients successfully, with complete clearance.[155]

A simple, prospective case series describing treatment of individual AKs with phenol 100% applied once a month for up to a maximum of 8 months in 32 patients reported no recurrence at 12 months.[37]

### 8.8 Combination treatment

There are many trials of combination therapy in the treatment of AK; they are of two kinds. The first is a serial approach where one treatment is advocated to follow the other depending on outcome, or as a specific regimen of pretreatment with the possibility that the effects of one treatment will maximize, or consolidate, the response. The second approach is to use a product with two active ingredients where, for instance, salicylic acid 10% may break down surface keratin and improve penetration and hence the efficacy of 5-FU 0·5% (see Section 8.2.1).

Salicylic acid ointment is sometimes used as a preliminary to topical 5-FU to remove overlying keratin. Salicylic acid 50% in croton oil has been described as a treatment for AKs when used in combination with TCA 20% and pretreatment with topical tretinoin as a serial regimen for facial peel.[39] The ointment base may be acting as an emollient, with some level of success for grade 1 AK[3,57] (see Section 8.1.1).

In a case series, patients were pretreated with diclofenac 3% gel for 12 weeks followed by cryosurgery for the 29% with residual lesions. This demonstrated an overall effective response to this combined management approach, with complete clearance maintained for 6–20 months (mean 10).[156] An open-label multicentre trial of cryosurgery (freeze time of 4–10 s) followed by diclofenac 3% gel 15 days later for the next 3 months vs. cryosurgery alone found that complete clearance increased from 21% to 46% with the addition of diclofenac. The clearance rates for a target lesion were greater at 32% vs. 64%.[157] A small, right–left-hand study with 4 weeks' pretreatment using diclofenac 3% gel and PDT compared with placebo gel and PDT demonstrated a greater decrease in the number and thickness of AKs on the side with diclofenac pretreatment, at 12 months.[158]

Diclofenac 3% as pretreatment for 5-FU 0·5% in 10% salicylic acid is also reported as an effective sequential regimen.[156] There are reports of 5–7 days of 5-FU 5% pretreatment also being safe and effective in combination with cryosurgery[110] or PDT[159] or, alternatively, in combination with glycolic peels.[38] PDT followed by imiquimod twice a week for 16 weeks was beneficial over PDT and subsequent vehicle cream alone when undertaken in a split-face study.[160] The complete clearance rate was not reported, but the percentage reduction in count was significant at 89·9% in the combined treatment side vs. 74·5% on the side treated with PDT alone. With PDT as the variable rather than imiquimod, PDT did not appear to improve the efficacy of imiquimod alone, although the study was small. Similarly, adding imiquimod 5% two times a week for 8 weeks to cryosurgery does not appear to improve on cryosurgery alone.

An alternative regimen has been studied for hypertrophic AKs on the forearms and the dorsa of the hands. Imiquimod 3·75% was used following a double, 5-s freeze–thaw cycle, randomized to the right or left arm and applied in up to two sachets per night for 2 weeks, followed by a 2-week break and a further 2 weeks. The comparison was cryosurgery alone on the other arm. Complete cure was not an end point, but there was a greater level of clearance in the combination arm (76%) than the control arm (38%). This difference did not emerge until 10 weeks after cryosurgery (4 weeks after completion of imiquimod), and maximized at the end of assessment at 14 weeks.[87] Randomizing to 5-FU 0·5%, 1 week after cryosurgery resulted in nonsignificant improvement over cryosurgery alone.[161]

**Key recommendations: physical and systemic therapies**

- Education at the outset of using physical therapies is important to ensure a full understanding of the side-effects, which can be marked and include scarring and altered pigmentation.
- Cryosurgery is a flexible and effective form of lesion-based physical therapy that removes the patient involvement in their own care and requires administration in a service with cryosurgery.
- Curettage can be warranted for thicker (grade 3) AKs, where they are resistant to topical therapy and where there is suspicion that they may represent early SCC. Histology must always be obtained. Diagnostic biopsy may be warranted on the same basis, but is subject to sampling error.
- PDT is an effective treatment for confluent AKs, such as on the scalp, which are difficult to manage or resistant to treatment in the absence of invasive disease.
- PDT has low scarring potential and less risk of poor healing in comparison with other physical therapies at vulnerable sites such as the lower leg.
- Pretreatment with topical therapy can increase the efficacy of physical therapies.
- Failure of an individual lesion to respond to physical therapy indicates a need for further evaluation. This could include formal excision.
- Systemic therapy is usually given in the context of multiple grade 3 AKs, a history of serial SCCs and immunosuppression. Therapy might be preventive with a retinoid and should be undertaken as part of a multidisciplinary decision, which might include alternatives such as the reduction of immunosuppression.

## 9.0 Special considerations

### 9.1 Body sites (strength of recommendation C, level of evidence 2+)

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 3. The scoring is based on the authors' evaluation of efficacy, ease of use, morbidity and cost-benefit.

#### 9.1.1 Periocular

The main consideration for treatment of periocular AK is the risk of adverse events involving the eye. All products licensed for treatment of AK have cautions in the PIL and/or summary of product characteristics concerning getting treatment in the eye. Creams used near the eye can smear into it, and inflammation caused by local destructive or inflammatory treatments such as cryosurgery may impinge upon the eye either directly or indirectly. Typically, liquid nitrogen is used with a contact probe, ensuring that cold vapour does not damage the eye.[162]

Studies undertaken in ophthalmology suggest that treatment is possible with close supervision. Treatment can be combined with care of the eye. In a case series of 14 patients treating periocular skin with 5-FU 5% twice daily for 2 weeks, antibiotic ointment was coprescribed and used until the area had healed.[163] Six of the 14 AKs were on the upper eyelid and nine abutted a lid margin. Five patients required a second course of treatment, but overall clearance was complete in all cases and remained so for a mean follow-up period of 38 months. Two patients had transient inflammatory side-effects affecting the eye. The potential precision of application of 5-FU 0·5% in 10% salicylic acid in a collodion base might make it a useful alternative to cream formulation, but there are no data on this.

A retrospective study of the use of imiquimod 5% cream for a range of periocular actinic lesions identified 47 patients mainly with AK, mainly on the lower lid.[164] Conjunctivitis occurred in 15 and six had ocular stinging, with conjunctivitis in three for over 2 weeks. Antibiotics were needed in three, for preseptal cellulitis in two of them. Nine patients discontinued imiquimod due to ocular irritation and conjunctivitis, of whom four patients recommenced and finished the treatment after a rest period. At a mean follow-up of 16 weeks, 34 (72%) patients had clinical clearance of the periocular lesions and no patient had any residual ophthalmic side-effects from imiquimod.

There is no good literature on diclofenac gel or ingenol mebutate, but both the PIL and product licence emphasize the importance of avoiding contact of the product with the eyes.

#### 9.1.2 Ears

The ear is a common site for the presentation of AK and SCC. The risk of metastasis is higher when SCC arises on the ear. This means that the context of treatment is slightly different at this site than at others. The wish to treat AK with a view to avoiding evolution to SCC may be a greater priority. Histological diagnosis of any thicker AKs to differentiate them from invasive SCC by shave biopsy or excision is recommended. These interventions may represent treatment of such AKs or a preliminary to treatment of SCC.

#### 9.1.3 Forearm and hands

Actinic keratoses on the dorsum of the hand are often multiple and hyperkeratotic. Early management with topical therapy or PDT may reduce the need for surgical interventions later. The skin is more tolerant of the side-effects of inflammatory treatments and hence permits prolongation of the course of treatment in some instances. This may be required due to the thicker skin or hindrance to treatment penetration by keratin in thicker AKs. Combinations of salicylic acid and 5-FU or curettage can be useful elements of treatment for the grade 3 AKs found on the forearm and back of hands (see Section 8.8)

#### 9.1.4 Below the knee

Actinic keratosis below the knee are often mixed with SCC *in situ*, a disposition to NMSC, including atypical BCCs and other actinic changes. They are a feature of elderly sun-exposed legs and often coincide with decreasing ability to heal. Treatments need to find the right balance between managing the disease and causing complications, which include nonhealing and soft-tissue infection. Treatment is likely to be intermittent, low intensity and chronic; most reports are case series with small numbers. Infrequent or pulsed application of 5-FU has been employed,[68] as has more intensive treatment using 5-FU chemowraps.[165] This entails the application of 5-FU 5% once a week under an occlusive bandage for 7 days over a period of 4–8 weeks. Gaps in treatment can be needed where skin breakage develops.

Diclofenac 3% gel might be employed with the expectation of fewer side-effects, but possibly less benefit. PDT is used on the lower legs, particularly where there may be problems with healing.

**Key recommendations: special sites (Table 2)**

- Poor healing sites such as below the knee in the elderly require flexible regimens, heightened supervision and consideration of less destructive treatments such as PDT.
- The ears are commonly affected by AK and require attention early in respect to all modalities of treatment, including preventive action with a broad-brimmed hat and sunscreen.
- Grade 3 AKs on the ear may warrant curettage early to obtain histology and avoid missed early SCC.
- The skin of the dorsum of the hands can be more resistant to treatment than the head and neck, and warrants extended periods of topical therapy.
- All licensed treatments include warnings about use near the eye. Periocular AK needs careful assessment in secondary care. Topical treatments may be possible, but clear guidance and supervision are needed.

### 9.2 Immunosuppressed patients

Data on the epidemiology and natural progression of AK in the immunosuppressed are less detailed than in the normal population. The risk of progression to SCC is likely to be higher, and therefore there is a greater need for treatment of AK. Wallingford *et al.* highlighted the need to monitor transplant patients with field-change AK disease.[166] Within a large cohort of renal transplant patients, nearly one-third were found to have AKs. Of these, half were isolated AKs and half were AKs within a field of AK and actinic change. In the subsequent year, the rate of development of SCC associated with the isolated AK was 7%, in comparison with 21% of those with field change, most of which (11 of 15) arose within the field. Other differences between the two groups were that the patients with isolated AKs tended to be transplanted later in life and had a shorter duration of immunosuppression.[166]

Anecdotal and limited trial data suggest that treatments for AKs in transplant patients are less effective than in the general population,[53] perhaps because AKs are more proliferative and hyperkeratotic in this group or because new lesions appear rapidly 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.[51] Where safety studies are undertaken in transplant patients they appear to demonstrate reactions similar to those in nontransplant patients.[167]

### 9.3 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 NMSC, such as organ transplant recipients, may warrant follow-up; the presence of at least 10 AKs is an indicator of this risk.[18]

Where treatments are likely to require evaluation and adjustment, follow-up in primary, intermediate or secondary care is needed. This could be by any member of the healthcare team with validated competencies in the safe and effective management of AK. Current NHS guidance suggests that patients with AK should be managed in primary care. Where this is a sole pathology and not complicated by NMSC or other factors, the patient should be provided with information to enable ongoing diagnosis and care.

### 9.4 Treatment failure

All treatments have some risk of failing to achieve clearance of an individual lesion. Where this is the case, the reason for failure needs assessment, where one of the possible explanations might be that the diagnosis is incorrect. Lesions within the differential diagnosis of AK include SCC *in situ*, invasive SCC, seborrhoeic keratosis, actinic porokeratosis, viral wart and others. Depending on the outcome of this clinical assessment, treatment might be escalated in intensity, duration or type, or the lesion might be biopsied or treated surgically.

An alternative interpretation of failure is that the patient continues to get new AKs. This is not true failure, but more an illustration of the nature of the disease. Once someone is diagnosed with AK, they are likely to need intermittent, lifelong treatment.

## 10.0 Economic considerations

Table 3 summarizes the cost-effectiveness of therapy.

It is likely that the number of treatment episodes for AK will increase. Australian Medicare data demonstrate an increase of 160% between 1994 and 2012 in claims for use of cryosurgery to treat 10 or more AKs. Many studies have tried to assess the cost-effectiveness of treatment for AK.[168–171] However, the methods of calculation and the different healthcare systems and their ways of funding prevent comparison.

Two nonindustry studies have been published from the U.K. Wilson tried to compare the cost of PDT and imiquimod, taking into account quality of life.[172] The author comments that a head-to-head study of imiquimod vs. PDT was required to enable more accurate calculations. Muston *et al.* used efficacy data from the literature to assess the cost–benefit ratio and reported that the costs and effectiveness of PDT compare well with other treatments for AK.[173]

At a practical local level, prescriptions that enable the patient to re-treat, extend treatment or treat new areas have an inherent economic value and enable the patient to exercise their judgement. Imiquimod and ingenol mebutate are dispensed in aliquot packages that are single-treatment doses and provided in a number to complete a course of treatment. This tightly defines the cost per course of treatment and the territory that can be treated. By contrast, Gibbs and Davis noted that patients used only 31% of the content of a tube of 5-FU 5% in a single course of treatment, which enables substantial flexibility in the course and territory of treatment.[174,175]

## 11.0 Future directions

Future directions need to address the human element of bearing the long-term diagnosis of AK and the technical challenges of treating AK effectively with low morbidity and acceptable cost. The clinical challenge comprises an ageing person with barely symptomatic dry areas of skin. Education, prevention and empowerment at this stage may help avoid the situation in 10–20 years where multiple untreated AKs accumulate and the patient presents with advanced AKs mingled with possible SCCs. The earliest stage in the prevention strategy shares ground with strategies for the avoidance of skin cancer, and equally shares its concerns of compromised vitamin D levels and loss of the indirect benefits of UV exposure. Collaborative work between patient groups and primary and secondary care should aim to find a suitable balanced approach to global care of patients with this diagnosis.

Technical assessment of the efficacy of treatments should continue, but using a standardized model of reporting. Review of data of AK treatment illustrates the variety of end points in studies, which makes comparison between them difficult. These include percentage clearance of lesion number within a person, percentage of people within a study having complete clearance, percentage of target lesions clearing, and mathematical models with projected AK behaviour based on within-study data.

The time points at which these measures are defined also vary and have the scope to alter the result greatly. Treatments have optimum times when their outcome is at its best, which can be up to 10 weeks after completion of treatment in the case of imiquimod. Equally, in the setting of a chronic relapsing and remitting disease, 12- and 24-month evaluation points are relevant. As AK is a multifocal manifestation of sun damage, AKs within a zone at 12 months may represent a mix of relapse and new lesions, which can further complicate quantitative assessment. Examples of all this are found in the studies referenced in this guideline.

Areas of uncertainty in the treatment of AK that require further studies include (i) measurement and relevance of vitamin D and (ii) prospective studies looking at the effect of treatment of AKs on subsequent SCC reduction.

## 12.0 Recommended audit points

In the last 20 consecutive patients with AK is there clear documentation of:

- the location of the AKs indicated on a drawing or a head and neck or body map;
- the grade or bulk of the AKs (e.g. grade 1, 2, 3 or descriptive; see Table 1);
- treatment modality and dosage;
- information (e.g. a PIL or other suitable source of information) provided to the patient on side-effects of treatment, where relevant;
- the patient having received information on the name and nature of their diagnosis;
- information provided for the GP in diagnosis and future management, in primary care where relevant.

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and to allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

## 13.0 Summary

The findings are summarized in Table 2. See the text for details of evidence.

Actinic keratoses are a multifocal manifestation of sun damage, comprising a spectrum of clinical complaint and pathology. They are relapsing and remitting and constitute a chronic disease. 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, therapy 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, shave or formal excision, may be 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 NMSC.

## Acknowledgments

We are very grateful to everyone who commented on the draft during the consultation period.

## References


1 Bell HK, Ormerod AD. Writing a British Association of Dermatologists clinical guideline: an update on the process and guidance for authors. *Br J Dermatol* 2009; **160**:725–8.

2 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839–42.

3 Olsen EA, Abernethy ML, Kulp-Shorten C *et al.* A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. *J Am Acad Dermatol* 1991; **24**:738–43.

4 Vatve M, Ortonne JP, Birch-Machin MA *et al.* Management of field change in actinic keratosis. *Br J Dermatol* 2007; **157**(Suppl. 2):21–4.

5 Freeman RG. Carcinogenic effects of solar radiation and prevention measures. *Cancer* 1968; **21**:1114–20.

6 Ziegler A, Jonason AS, Leffell DJ *et al.* Sunburn and p53 in the onset of skin cancer. *Nature* 1994; **372**:773–6.

7 Barr BB, Benton EC, McLaren K *et al.* Papillomavirus infection and skin cancer in renal allograft recipients. *Lancet* 1989; **2**:224–5.

8 Baudouin C, Charveron M, Tarroux R *et al.* Environmental pollutants and skin cancer. *Cell Biol Toxicol* 2002; **18**:341–8.

9 Wong ST, Chan HL, Teo SK. The spectrum of cutaneous and internal malignancies in chronic arsenic toxicity. *Singapore Med J* 1998; **39**:171–3.

10 Norris JF. Sunscreens, suntans, and skin cancer. Local councils should remove sunbeds from leisure centres. *BMJ* 1996; **313**:941–2.

11 Bajdik CD, Gallagher RP, Astrakianakis G *et al.* Non-solar ultraviolet radiation and the risk of basal and squamous cell skin cancer. *Br J Cancer* 1996; **73**:1612–4.

12 Roest MA, Keane FM, Agnew K *et al.* Multiple squamous skin carcinomas following excess sunbed use. *J R Soc Med* 2001; **94**:636–7.

13 Atkins D, Bang RH, Sternberg MR *et al.* Reliable methods to evaluate the burden of actinic keratoses. *J Invest Dermatol* 2006; **126**:591–4.

14 O'Beirn SFO, Judge P, Maccon CF *et al.* Skin cancer in County Galway, Ireland. In: *Proceedings of the Sixth National Cancer Conference, sponsored by the American Cancer Society Inc. and the National Cancer Institute, September 1968*. Philadelphia: Lippincott, 1970; 489–500.

15 Harvey I, Frankel S, Marks R *et al.* Non-melanoma skin cancer and solar keratoses. I. Methods and descriptive results of the South Wales Skin Cancer Study. *Br J Cancer* 1996; **74**:1302–7.

16 Memon AA, Tomenson JA, Bothwell J *et al.* Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol* 2000; **142**:1154–9.

17 Eder J, Prillinger K, Korn A *et al.* Prevalence of actinic keratosis among dermatology outpatients in Austria. *Br J Dermatol* 2014; **171**:1415–21.

18 Flohil SC, van der Leest RJ, Dowlatshahi EA *et al.* Prevalence of actinic keratosis and its risk factors in the general population: the Rotterdam Study. *J Invest Dermatol* 2013; **133**:1971–8.

19 Marks R, Foley P, Goodman G *et al.* Spontaneous remission of solar keratoses: the case for conservative management. *Br J Dermatol* 1986; **115**:649–55.

20 Criscione VD, Weinstock MA, Naylor MF *et al.* Actinic keratoses: natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer* 2009; **115**:2523–30.

21 Marks R, Rennie G, Selwood TS. Malignant transformation of solar keratoses to squamous cell carcinoma. *Lancet* 1988; **1**:795–7.

22 Dodson JM, DeSpain J, Hewett JE *et al.* Malignant potential of actinic keratoses and the controversy over treatment. A patient-oriented perspective. *Arch Dermatol* 1991; **127**:1029–31.

23 Foote JA, Harris RB, Giuliano AR *et al.* Predictors for cutaneous basal- and squamous-cell carcinoma among actinically damaged adults. *Int J Cancer* 2001; **95**:7–11.

24 Chen GJ, Feldman SR, Williford PM *et al.* Clinical diagnosis of actinic keratosis identifies an elderly population at high risk of developing skin cancer. *Dermatol Surg* 2005; **31**:43–7.

25 Lambert SR, Mladkova N, Gulati A *et al.* Key differences identified between actinic keratosis and cutaneous squamous cell carcinoma by transcriptome profiling. *Br J Cancer* 2014; **110**:520–9.

26 Werner RN, Sammain A, Erdmann R *et al.* The natural history of actinic keratosis: a systematic review. *Br J Dermatol* 2013; **169**:502–18.

27 Janda M. Teledermatology: its use in the detection and management of actinic keratosis. *Curr Probl Dermatol* 2015; **46**:101–7.

28 Huerta-Brogeras M, Olmos O, Borbujo J *et al.* Validation of dermoscopy as a real-time noninvasive diagnostic imaging technique for actinic keratosis. *Arch Dermatol* 2012; **148**:1159–64.

29 Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. Available at: www.sign.ac.uk/pdf/sign116.pdf (last accessed 16 September 2016).

30 Shigaki C, Kruse RL, Mehr D *et al.* Motivation and diabetes self-management. *Chronic Illn* 2010; **6**:202–14.

31 Stockfleth E. The paradigm shift in treating actinic keratosis: a comprehensive strategy. *J Drugs Dermatol* 2012; **11**:1462–7.

32 Gupta AK, Paquet M, Villanueva E *et al.* Interventions for actinic keratoses. *Cochrane Database Syst Rev* 2012; **12**:CD004415.

33 Esmann S, Vinding GR, Christensen KB *et al.* Assessing the influence of actinic keratosis on patients' quality of life: the AKQoL questionnaire. *Br J Dermatol* 2013; **168**:277–83.

34 Esmann S. Patients' perspectives on actinic keratosis. *Curr Probl Dermatol* 2015; **46**:8–13.

35 Pomerantz H, Hogan D, Eilers D *et al.* Long-term efficacy of topical fluorouracil cream, 5%, for treating actinic keratosis: a randomized clinical trial. *JAMA Dermatol* 2015; **151**:952–60.

36 Witheiler DD, Lawrence N, Cox SE *et al.* Long-term efficacy and safety of Jessner's solution and 35% trichloroacetic acid versus 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Dermatol Surg* 1997; **23**:191–6.

37 Kaminaka C, Yamamoto Y, Yonei N *et al.* Phenol peels as a novel therapeutic approach for actinic keratosis and Bowen disease: prospective pilot trial with assessment of clinical, histologic, and immunohistochemical correlations. *J Am Acad Dermatol* 2009; **60**:615–25.

38 Ditre CM. Treatment of actinic keratosis and photodamaged skin with 5-fluorouracil 5% cream and glycolic acid peels. *Cosmet Dermatol* 2004; **17**:25–7.

39 Swinehart JM. Salicylic acid ointment peeling of the hands and forearms. Effective nonsurgical removal of pigmented lesions and actinic damage. *J Dermatol Surg Oncol* 1992; **18**:495–8.

40 Werner RN, Stockfleth E, Connolly SM *et al.* Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum – short version. *J Eur Acad Dermatol Venereol* 2015; **29**:2069–79.

41 National Institute for Health and Care Excellence. Improving outcomes for people with skin tumours including melanoma. Available at: https://www.nice.org.uk/guidance/csg8 (last accessed 16 September 2016).

42 Chetty P, Choi F, Mitchell T. Primary care review of actinic keratosis and its therapeutic options: a global perspective. *Dermatol Ther (Heidelb)* 2015; **5**:19–35.

43 Englert C, Hughes B. A review of actinic keratosis for the nurse practitioner: diagnosis, treatment, and clinical pearls. *J Am Acad Nurse Pract* 2012; **24**:290–6.

44 Primary Care Dermatology Society. Actinic (solar) keratosis: primary care treatment pathway. Available at: http://www.pcds.org.uk/ee/images/uploads/general/Actinic_%28Solar%29_Keratosis_Primary_Care_Treatment_Pathway.pdf (last accessed 16 September 2016).

45 Primary Care Dermatology Society. Actinic keratosis (syn. solar keratosis). Available at: http://www.pcds.org.uk/clinical-guidance/actinic-keratosis-syn.-solar-keratosis (last accessed 16 September 2016).

46 Thompson SC, Jolley D, Marks R. Reduction of solar keratoses by regular sunscreen use. *N Engl J Med* 1993; **329**:1147–51.

47 Naylor MF, Boyd A, Smith DW *et al.* High sun protection factor sunscreens in the suppression of actinic neoplasia. *Arch Dermatol* 1995; **131**:170–5.

48 Green A, Williams G, Neale R *et al.* Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomised controlled trial. *Lancet* 1999; **354**:723–9.

49 Ulrich C, Jurgensen JS, Degen A *et al.* Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case–control study. *Br J Dermatol* 2009; **161**(Suppl. 3):78–84.

50 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**:1681–91.

51 de Graaf YG, Kennedy C, Wolterbeek R *et al.* Photodynamic therapy does not prevent cutaneous squamous-cell carcinoma in organ-transplant recipients: results of a randomized-controlled trial. *J Invest Dermatol* 2006; **126**:569–74.

52 Harwood CA, Mesher D, McGregor JM *et al.* A surveillance model for skin cancer in organ transplant recipients: a 22-year prospective study in an ethnically diverse population. *Am J Transplant* 2013; **13**:119–29.

53 Dragieva G, Hafner J, Dummer R *et al.* Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004; **77**:115–21.

54 McNamara IR, Muir J, Galbraith AJ. Acitretin for prophylaxis of cutaneous malignancies after cardiac transplantation. *J Heart Lung Transplant* 2002; **21**:1201–5.

55 Jirakulaporn T, Endrizzi B, Lindgren B *et al.* Capecitabine for skin cancer prevention in solid organ transplant recipients. *Clin Transplant* 2011; **25**:541–8.

56 Black HS, Herd JA, Goldberg LH *et al.* Effect of a low-fat diet on the incidence of actinic keratosis. *N Engl J Med* 1994; **330**:1272–5.

57 Rivers JK, Arlette J, Shear N *et al.* Topical treatment of actinic keratoses with 3.0% diclofenac in 2.5% hyaluronan gel. *Br J Dermatol* 2002; **146**:94–100.

58 Akarsu S, Aktan S, Atahan A *et al.* Comparison of topical 3% diclofenac sodium gel and 5% imiquimod cream for the treatment of actinic keratoses. *Clin Exp Dermatol* 2011; **36**:479–84.

59 Szeimies RM, Gerritsen MJ, Gupta G *et al.* Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol* 2004; **51**:547–55.

60 Jorizzo J, Dinehart S, Matheson R *et al.* Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. *J Am Acad Dermatol* 2007; **57**:265–8.

61 Darlington S, Williams G, Neale R *et al.* A randomized controlled trial to assess sunscreen application and beta carotene supplementation in the prevention of solar keratoses. *Arch Dermatol* 2003; **139**:451–5.

62 Eaglstein WH, Weinstein GD, Frost P. Fluorouracil: mechanism of action in human skin and actinic keratoses. I. Effect on DNA synthesis *in vivo*. *Arch Dermatol* 1970; **101**:132–9.

63 Ingenol mebutate (Picato) for actinic keratosis. *Med Lett Drugs Ther* 2012; **54**:35–6.

64 Stockfleth E, Kerl H, Zwingers T *et al.* Low-dose 5-fluorouracil in combination with salicylic acid as a new lesion-directed option to treat topically actinic keratoses: histological and clinical study results. *Br J Dermatol* 2011; **165**:1101–8.

65 Gupta AK, Paquet M. Network meta-analysis of the outcome 'participant complete clearance' in non-immunosuppressed participants of eight interventions for actinic keratosis: a follow-up on a Cochrane review. *Br J Dermatol* 2013; **169**:250–9.

66 Kurwa HA, Yong-Gee SA, Seed PT *et al.* A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. *J Am Acad Dermatol* 1999; **41**:414–8.

67 Robinson TA, Kligman AM. Treatment of solar keratoses of the extremities with retinoic acid and 5-fluorouracil. *Br J Dermatol* 1975; **92**:703–6.

68 Pearlman DL. Weekly pulse dosing: effective and comfortable topical 5-fluorouracil treatment of multiple facial actinic keratoses. *J Am Acad Dermatol* 1991; **25**:665–7.

69 Epstein E. Does intermittent 'pulse' topical 5-fluorouracil therapy allow destruction of actinic keratoses without significant inflammation? *J Am Acad Dermatol* 1998; **38**:77–80.

70 Jury CS, Ramraka-Jones VS, Gudi V *et al.* A randomized trial of topical 5% 5-fluorouracil (Efudix cream) in the treatment of actinic keratoses comparing daily with weekly treatment. *Br J Dermatol* 2005; **153**:808–10.

71 Schlaak M, Simon JC. Topical treatment of actinic keratoses with low-dose 5-fluorouracil in combination with salicylic acid – pilot study. *J Dtsch Dermatol Ges* 2010; **8**:174–8.

72 Stockfleth E, Zwingers T, Willers C. Recurrence rates and patient assessed outcomes of 0.5% 5-fluorouracil in combination with salicylic acid treating actinic keratoses. *Eur J Dermatol* 2012; **22**:370–4.

73 Szeimies RM, Dirschka T, Prechtl A *et al.* Efficacy of low-dose 5-fluorouracil/salicylic acid in actinic keratoses in relation to treatment duration. *J Dtsch Dermatol Ges* 2015; **13**:430–8.

74 Hadley G, Derry S, Moore RA. Imiquimod for actinic keratosis: systematic review and meta-analysis. *J Invest Dermatol* 2006; **126**:1251–5.

75 Stockfleth E, Meyer T, Benninghoff B *et al.* A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol* 2002; **138**:1498–502.

76 Korman N, Moy R, Ling M *et al.* Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol* 2005; **141**:467–73.

77 Alomar A, Bichel J, McRae S. Vehicle-controlled, randomized, double-blind study to assess safety and efficacy of imiquimod 5% cream applied once daily 3 days per week in one or two courses of treatment of actinic keratoses on the head. *Br J Dermatol* 2007; **157**:133–41.

78 Foley P, Merlin K, Cumming S *et al.* A comparison of cryotherapy and imiquimod for treatment of actinic keratoses: lesion clearance, safety, and skin quality outcomes. *J Drugs Dermatol* 2011; **10**:1432–8.

79 Pini AM, Koch S, Scharer L *et al.* Eruptive keratoacanthoma following topical imiquimod for *in situ* squamous cell carcinoma of the skin in a renal transplant recipient. *J Am Acad Dermatol* 2008; **59**(5 Suppl.):S116–7.

80 Serra-Guillen C, Nagore E, Hueso L *et al.* A randomized comparative study of tolerance and satisfaction in the treatment of actinic keratosis of the face and scalp between 5% imiquimod cream and photodynamic therapy with methyl aminolaevulinate. *Br J Dermatol* 2011; **164**:429–33.

81 Krawtchenko N, Roewert-Huber J, Ulrich M *et al.* A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol* 2007; **157**(Suppl. 2):34–40.

82 Lee PK, Harwell WB, Loven KH *et al.* Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg* 2005; **31**:659–64.

83 Hanke CW, Beer KR, Stockfleth E *et al.* Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. *J Am Acad Dermatol* 2010; **62**:573–81.

84 Hanke CW, Swanson N, Bruce S *et al.* Complete clearance is sustained for at least 12 months after treatment of actinic keratoses of the face or balding scalp via daily dosing with imiquimod 3.75% or 2.5% cream. *J Drugs Dermatol* 2011; **10**:165–70.

85 Swanson N, Abramovits W, Berman B *et al.* Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010; **62**:582–90.

86 Jorizzo JL, Markowitz O, Lebwohl MG *et al.* A randomized, double-blinded, placebo-controlled, multicenter, efficacy and safety study of 3.75% imiquimod cream following cryosurgery for the treatment of actinic keratoses. *J Drugs Dermatol* 2010; **9**:1101–8.

87 Goldenberg G, Linkner RV, Singer G *et al.* An investigator-initiated study to assess the safety and efficacy of imiquimod 3.75% cream when used after cryotherapy in the treatment of hypertrophic actinic keratoses on dorsal hands and forearms. *J Clin Aesthet Dermatol* 2013; **6**:36–43.

88 Smith SR, Morhenn VB, Piacquadio DJ. Bilateral comparison of the efficacy and tolerability of 3% diclofenac sodium gel and 5% 5-fluorouracil cream in the treatment of actinic keratoses of the face and scalp. *J Drugs Dermatol* 2006; **5**:156–9.

89 Segatto MM, Dornelles SI, Silveira VB *et al.* Comparative study of actinic keratosis treatment with 3% diclofenac sodium and 5% 5-fluorouracil. *An Bras Dermatol* 2013; **88**:732–8.

90 Wolf JE, Taylor JR, Tschen E *et al.* Topical 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001; **40**:709–13.

91 Pflugfelder A, Welter AK, Leiter U *et al.* Open label randomized study comparing 3 months vs. 6 months treatment of actinic keratoses with 3% diclofenac in 2.5% hyaluronic acid gel: a trial of the German Dermatologic Cooperative Oncology Group. *J Eur Acad Dermatol Venereol* 2012; **26**:48–53.

92 Anderson L, Schmieder GJ, Werschler WP *et al.* Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for actinic keratosis. *J Am Acad Dermatol* 2009; **60**:934–43.

93 Lebwohl M, Swanson N, Anderson LL *et al.* Ingenol mebutate gel for actinic keratosis. *N Engl J Med* 2012; **366**:1010–9.

94 Lebwohl M, Shumack S, Stein Gold L *et al.* Long-term follow-up study of ingenol mebutate gel for the treatment of actinic keratoses. *JAMA Dermatol* 2013; **149**:666–70.

95 Garbe C, Basset-Seguin N, Poulin Y *et al.* Efficacy and safety of follow-up field treatment of actinic keratosis with ingenol mebutate 0.015% gel: a randomized, controlled 12-month study. *Br J Dermatol* 2016; **174**:505–13.

96 Anderson L, Melgaard A, Schmeider G *et al.* Two-day topical treatment with ingenol mebutate gel, 0.05% for actinic keratoses on the trunk and extremities: analysis of data pooled from two trials. *J Am Acad Dermatol* 2012; **66**:AB159.

97 US Food and Drug Administration. Picato (ingenol mebutate) gel: drug safety communication – FDA warns of severe adverse events, requires label changes. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm459311.htm (last accessed 16 September 2016).

98 Ku J. Clinical review. NDA 202833. PICATO™ (ingenol mebutate gel, PEP005 gel). Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202833Orig1s000MedR.pdf (last accessed 16 September 2016).

99 Erlendsson AM, Karmisholt KE, Haak CS *et al.* Topical corticosteroid has no influence on inflammation or efficacy after ingenol mebutate treatment of grade I to III actinic keratoses (AK): a randomized clinical trial. *J Am Acad Dermatol* 2016; **74**:709–15.

100 Ianhez M, Fleury LF Jr, Miot HA *et al.* Retinoids for prevention and treatment of actinic keratosis. *An Bras Dermatol* 2013; **88**:585–93.

101 Kang S, Goldfarb MT, Weiss JS *et al.* Assessment of adapalene gel for the treatment of actinic keratoses and lentigines: a randomized trial. *J Am Acad Dermatol* 2003; **49**:83–90.

102 Weinstock MA, Bingham SF, Lew RA *et al.* Topical tretinoin therapy and all-cause mortality. *Arch Dermatol* 2009; **145**:18–24.

103 Thai KE, Fergin P, Freeman M *et al.* A prospective study of the use of cryosurgery for the treatment of actinic keratoses. *Int J Dermatol* 2004; **43**:687–92.

104 Szeimies RM, Karrer S, Radakovic-Fijan S *et al.* Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; **47**:258–62.

105 Freeman M, Vinciullo C, Francis D *et al.* A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat* 2003; **14**:99–106.

106 Kaufmann R, Spelman L, Weightman W *et al.* Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol* 2008; **158**:994–9.

107 Morton C, Campbell S, Gupta G *et al.* Intraindividual, right–left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol* 2006; **155**:1029–36.

108 Chiarello SE. Cryopeeling (extensive cryosurgery) for treatment of actinic keratoses: an update and comparison. *Dermatol Surg* 2000; **26**:728–32.

109 Abadir DM. Combination of topical 5-fluorouracil with cryotherapy for treatment of actinic keratoses. *J Dermatol Surg Oncol* 1983; **9**:403–4.

110 Jorizzo J, Weiss J, Furst K *et al.* Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery: a randomized, vehicle-controlled clinical trial. *Arch Dermatol* 2004; **140**:813–6.

111 Motley R, Kersey P, Lawrence C *et al.* Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol* 2002; **146**:18–25.

112 Moriarty M, Dunn J, Darragh A *et al.* Etretinate in treatment of actinic keratosis. A double-blind crossover study. *Lancet* 1982; **1**:364–5.

113 Watson AB. Preventative effect of etretinate therapy on multiple actinic keratoses. *Cancer Detect Prev* 1986; **9**:161–5.

114 Smit JV, de Sevaux RG, Blokx WA *et al.* Acitretin treatment in (pre)malignant skin disorders of renal transplant recipients:


 

histologic and immunohistochemical effects. *J Am Acad Dermatol* 2004; **50**:189–96.
115 EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: long-term management of the transplant recipient. IV.6.2. Cancer risk after renal transplantation. Skin cancers: prevention and treatment. *Nephrol Dial Transplant* 2002; **17**:S31–6.
116 Kovach BT, Murphy G, Otley CC *et al.* Oral retinoids for chemoprevention of skin cancers in organ transplant recipients: results of a survey. *Transplant Proc* 2006; **38**:1366–8.
117 Elmets CA, Viner JL, Pentland AP *et al.* Chemoprevention of nonmelanoma skin cancer with celecoxib: a randomized, double-blind, placebo-controlled trial. *J Natl Cancer Inst* 2010; **102**:1835–44.
118 Liebman TN, Stein JA, Polsky D. Cyclo-oxygenase-2 inhibitors for chemoprevention of nonmelanoma skin cancer: is there a role for these agents? *J Am Acad Dermatol* 2013; **68**:173–6.
119 Dirschka T, Radny P, Dominicus R *et al.* Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. *Br J Dermatol* 2012; **166**:137–46.
120 Szeimies RM, Radny P, Sebastian M *et al.* Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. *Br J Dermatol* 2010; **163**:386–94.
121 Morton CA, Szeimies RM, Sidoroff A *et al.* European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; **27**:536–44.
122 Klein A, Karrer S, Horner C *et al.* Comparing cold-air analgesia, systemically administered analgesia and scalp nerve blocks for pain management during photodynamic therapy for actinic keratosis of the scalp presenting as field cancerization: a randomized controlled trial. *Br J Dermatol* 2015; **173**:192–200.
123 Petersen B, Wiegell SR, Wulf HC. Light protection of the skin after photodynamic therapy reduces inflammation: an unblinded randomized controlled study. *Br J Dermatol* 2014; **171**:175–8.
124 Tarstedt M, Rosdahl I, Berne B *et al.* A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix®)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005; **85**:424–8.
125 Piacquadio DJ, Chen DM, Farber HF *et al.* Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. *Arch Dermatol* 2004; **140**:41–6.
126 Taub AF, Garretson CB. A randomized, blinded, bilateral intraindividual, vehicle-controlled trial of the use of photodynamic therapy with 5-aminolevulinic acid and blue light for the treatment of actinic keratoses of the upper extremities. *J Drugs Dermatol* 2011; **10**:1049–56.
127 Tschen EH, Wong DS, Pariser DM *et al.* Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol* 2006; **155**:1262–9.
128 Sotiriou E, Apalla Z, Chovarda E *et al.* Single vs. fractionated photodynamic therapy for face and scalp actinic keratoses: a randomized, intraindividual comparison trial with 12-month follow-up. *J Eur Acad Dermatol Venereol* 2012; **26**:36–40.
129 Togsverd-Bo K, Haak CS, Thaysen-Petersen D *et al.* Intensified photodynamic therapy of actinic keratoses with fractional $CO_2$ laser: a randomized clinical trial. *Br J Dermatol* 2012; **166**:1262–9.
130 Scola N, Terras S, Georgas D *et al.* A randomized, half-side comparative study of aminolaevulinate photodynamic therapy vs. $CO_2$ laser ablation in immunocompetent patients with multiple actinic keratoses. *Br J Dermatol* 2012; **167**:1366–73.
131 Patel G, Armstrong AW, Eisen DB. Efficacy of photodynamic therapy versus other interventions in randomized clinical trials for the treatment of actinic keratoses: a systematic review and meta-analysis. *JAMA Dermatol* 2014; **150**:1281–8.
132 Serra-Guillen C, Nagore E, Hueso L *et al.* A randomized pilot comparative study of topical methyl aminolevulinate photodynamic therapy versus imiquimod 5% versus sequential application of both therapies in immunocompetent patients with actinic keratosis: clinical and histologic outcomes. *J Am Acad Dermatol* 2012; **66**:e131–7.
133 Hadley J, Tristani-Firouzi P, Hull C *et al.* Results of an investigator-initiated single-blind split-face comparison of photodynamic therapy and 5% imiquimod cream for the treatment of actinic keratoses. *Dermatol Surg* 2012; **38**:722–7.
134 Sotiriou E, Apalla Z, Maliamani F *et al.* Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol* 2009; **23**:1061–5.
135 Hauschild A, Stockfleth E, Popp G *et al.* Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. *Br J Dermatol* 2009; **160**:1066–74.
136 Szeimies RM, Stockfleth E, Popp G *et al.* Long-term follow-up of photodynamic therapy with a self-adhesive 5-aminolaevulinic acid patch: 12 months data. *Br J Dermatol* 2010; **162**:410–4.
137 Wiegell SR, Haedersdal M, Philipsen PA *et al.* Continuous activation of PpIX by daylight is as effective as and less painful than conventional photodynamic therapy for actinic keratoses; a randomized, controlled, single-blinded study. *Br J Dermatol* 2008; **158**:740–6.
138 Wiegell SR, Haedersdal M, Eriksen P *et al.* Photodynamic therapy of actinic keratoses with 8% and 16% methyl aminolaevulinate and home-based daylight exposure: a double-blinded randomized clinical trial. *Br J Dermatol* 2009; **160**:1308–14.
139 Wiegell SR, Fabricius S, Stender IM *et al.* A randomized, multicentre study of directed daylight exposure times of 1½ vs. 2½ h in daylight-mediated photodynamic therapy with methyl aminolaevulinate in patients with multiple thin actinic keratoses of the face and scalp. *Br J Dermatol* 2011; **164**:1083–90.
140 Rubel DM, Spelman L, Murrell DF *et al.* Daylight photodynamic therapy with methyl aminolevulinate cream as a convenient, similarly effective, nearly painless alternative to conventional photodynamic therapy in actinic keratosis treatment: a randomized controlled trial. *Br J Dermatol* 2014; **171**:1164–71.
141 Lacour JP, Ulrich C, Gilaberte Y *et al.* Daylight photodynamic therapy with methyl aminolevulinate cream is effective and nearly painless in treating actinic keratoses: a randomised, investigator-blinded, controlled, phase III study throughout Europe. *J Eur Acad Dermatol Venereol* 2015; **29**:2342–8.
142 Morton CA, Wulf HC, Szeimies RM *et al.* Practical approach to the use of daylight photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: a European consensus. *J Eur Acad Dermatol Venereol* 2015; **29**:1718–23.
143 See JA, Shumack S, Murrell DF *et al.* Consensus recommendations on the use of daylight photodynamic therapy with methyl aminolevulinate cream for actinic keratoses in Australia. *Australas J Dermatol* 2016; **57**:167–74.
144 Wiegell SR, Wulf HC, Szeimies RM *et al.* Daylight photodynamic therapy for actinic keratosis: an international consensus:

International Society for Photodynamic Therapy in Dermatology. *J Eur Acad Dermatol Venereol* 2012; **26**:673–9.
145 Genovese G, Fai D, Fai C *et al.* Daylight methyl-aminolevulinate photodynamic therapy versus ingenol mebutate for the treatment of actinic keratoses: an intraindividual comparative analysis. *Dermatol Ther* 2016; **29**:191–6.
146 de Vries K, Prens EP. Laser treatment and its implications for photodamaged skin and actinic keratosis. *Curr Probl Dermatol* 2015; **46**:129–35.
147 Ostertag JU, Quaedvlieg PJ, van der Geer S *et al.* A clinical comparison and long-term follow-up of topical 5-fluorouracil versus laser resurfacing in the treatment of widespread actinic keratoses. *Lasers Surg Med* 2006; **38**:731–9.
148 Hantash BM, Stewart DB, Cooper ZA *et al.* Facial resurfacing for nonmelanoma skin cancer prophylaxis. *Arch Dermatol* 2006; **142**:976–82.
149 Sherry SD, Miles BA, Finn RA. Long-term efficacy of carbon dioxide laser resurfacing for facial actinic keratosis. *J Oral Maxillofac Surg* 2007; **65**:1135–9.
150 Iyer S, Friedli A, Bowes L *et al.* Full face laser resurfacing: therapy and prophylaxis for actinic keratoses and non-melanoma skin cancer. *Lasers Surg Med* 2004; **34**:114–9.
151 Ostertag JU, Quaedvlieg PJF, Neumann MHAM, Krekels GA. Recurrence rates and long-term follow-up after laser resurfacing as a treatment for widespread actinic keratoses in the face and on the scalp. *Dermatol Surg* 2006; **32**:261–7.
152 Gan SD, Hsu SH, Chuang G *et al.* Ablative fractional laser therapy for the treatment of actinic keratosis: a split-face study. *J Am Acad Dermatol* 2016; **74**:387–9.
153 Prens SP, de Vries K, Neumann HA *et al.* Non-ablative fractional resurfacing in combination with topical tretinoin cream as a field treatment modality for multiple actinic keratosis: a pilot study and a review of other field treatment modalities. *J Dermatolog Treat* 2013; **24**:227–31.
154 Coleman WP, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg* 1996; **22**:17–21.
155 Winton GB, Salasche SJ. Dermabrasion of the scalp as a treatment for actinic damage. *J Am Acad Dermatol* 1986; **14**:661–8.
156 Mastrolonardo M. Topical diclofenac 3% gel plus cryotherapy for treatment of multiple and recurrent actinic keratoses. *Clin Exp Dermatol* 2009; **34**:33–5.
157 Berlin JM, Rigel DS. Diclofenac sodium 3% gel in the treatment of actinic keratoses postcryosurgery. *J Drugs Dermatol* 2008; **7**:669–73.
158 Van der Geer S, Krekels GA. Treatment of actinic keratoses on the dorsum of the hands: ALA-PDT versus diclofenac 3% gel followed by ALA-PDT. A placebo-controlled, double-blind, pilot study. *J Dermatolog Treat* 2009; **20**:259–65.
159 Gilbert DJ. Treatment of actinic keratoses with sequential combination of 5-fluorouracil and photodynamic therapy. *J Drugs Dermatol* 2005; **4**:161–3.
160 Shaffelburg M. Treatment of actinic keratoses with sequential use of photodynamic therapy; and imiquimod 5% cream. *J Drugs Dermatol* 2009; **8**:35–9.
161 Hoover WD 3rd, Jorizzo JL, Clark AR *et al.* Efficacy of cryosurgery and 5-fluorouracil cream 0.5% combination therapy for the treatment of actinic keratosis. *Cutis* 2014; **94**:255–9.
162 Tuppurainen K. Cryotherapy for eyelid and periocular basal cell carcinomas: outcome in 166 cases over an 8-year period. *Graefes Arch Clin Exp Ophthalmol* 1995; **233**:205–8.
163 Couch SM, Custer PL. Topical 5-fluorouracil for the treatment of periocular actinic keratosis and low-grade squamous malignancy. *Ophthal Plast Reconstr Surg* 2012; **28**:181–3.
164 Cannon PS, O'Donnell B, Huilgol SC *et al.* The ophthalmic side-effects of imiquimod therapy in the management of periocular skin lesions. *Br J Ophthalmol* 2011; **95**:1682–5.
165 Tallon B, Turnbull N. 5% Fluorouracil chemowraps in the management of widespread lower leg solar keratoses and squamous cell carcinoma. *Australas J Dermatol* 2013; **54**:313–6.
166 Wallingford SC, Russell SA, Vail A *et al.* Actinic keratoses, actinic field change and associations with squamous cell carcinoma in renal transplant recipients in Manchester, U.K. *Acta Derm Venereol* 2015; **95**:830–4.
167 Ingham AI, Weightman W. The efficacy and safety of topical 5% 5-fluorouracil in renal transplant recipients for the treatment of actinic keratoses. *Australas J Dermatol* 2014; **55**:204–8.
168 Annemans L, Caekelbergh K, Roelandts R *et al.* Real-life practice study of the clinical outcome and cost-effectiveness of photodynamic therapy using methyl aminolevulinate (MAL-PDT) in the management of actinic keratosis and basal cell carcinoma. *Eur J Dermatol* 2008; **18**:539–46.
169 Caekelbergh K, Annemans L, Lambert J *et al.* Economic evaluation of methyl aminolaevulinate-based photodynamic therapy in the management of actinic keratosis and basal cell carcinoma. *Br J Dermatol* 2006; **155**:784–90.
170 Colombo GL, Chimenti S, Di Matteo S *et al.* Cost-effectiveness analysis of topical treatments for actinic keratosis in the perspective of the Italian health care system. *G Ital Dermatol Venereol* 2010; **145**:573–81.
171 Gold MH. Pharmacoeconomic analysis of the treatment of multiple actinic keratoses. *J Drugs Dermatol* 2008; **7**:23–5.
172 Wilson EC. Cost effectiveness of imiquimod 5% cream compared with methyl aminolevulinate-based photodynamic therapy in the treatment of non-hyperkeratotic, non-hypertrophic actinic (solar) keratoses: a decision tree model. *Pharmacoeconomics* 2010; **28**:1055–64.
173 Muston D, Downs A, Rives V. An economic evaluation of topical treatments for actinic keratosis. *J Dermatolog Treat* 2009; **20**:266–75.
174 Gibbs S, Davis T. Usage and patient experience of 5% fluorouracil cream. *Clin Exp Dermatol* 2015; **40**:88.
175 Perera E, McGuigan S, Sinclair R. Cost for the treatment of actinic keratosis on the rise in Australia. *F1000Res* 2014; **3**:184.
176 Pariser DM, Lowe NJ, Stewart DM *et al.* Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol* 2003; **48**:227–32.
177 Colechin E, Sims A, Reay C *et al.* Ambulight photodynamic therapy. Available at: http://www.nice.org.uk/guidance/mtg6/documents/ambulight-photodynamic-therapy-for-the-treatment-of-nonmelanoma-skin-cancer-external-assessment-centre-report2 (last accessed 16 September 2016).
178 Gov.uk. National tariff payment system 2014/15. Available at: https://www.gov.uk/government/publications/national-tariff-payment-system-2014-to-2015. (last accessed 16 September 2016).
179 Personal Social Services Research Unit. Unit costs of health and social care 2015. Available at: http://www.pssru.ac.uk/project-pages/unit-costs/2015 (last accessed 16 September 2016).

## Supporting information

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

**Appendix S1.** Search strategy.

## Appendix 1

Levels of evidence

| Level of evidence | Type of evidence |
|---|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias |
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1− | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a] |
| 2++ | High-quality systematic reviews of case–control or cohort studies. High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance, and a moderate probability that the relationship is causal |
| 2− | Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal[a] |
| 3 | Nonanalytical studies (for example case reports, case series) |
| 4 | Expert opinion, formal consensus |

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

## Appendix 2

Strengths of recommendation

| Class | Evidence |
|---|---|
| A | At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or<br>A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results, or<br>Evidence drawn from a NICE technology appraisal |
| B | A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or<br>Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or<br>Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4, or<br>Extrapolated evidence from studies rated as 2+, or<br>Formal consensus |
| D (GPP) | A good practice point (GPP) is a recommendation for best practice based on the experience of the Guideline Development Group |

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.