Structured Expert Consensus on Actinic Keratosis

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Structured expert consensus on actinic keratosis: treatment algorithm focusing on daylight PDT

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Abstract

Background: A practical and up-to-date consensus among experts is paramount to further improve patient care in actinic keratosis (AK).

Objectives: To develop a structured consensus statement on the diagnosis, classification and practical management of AK based on up-to-date information.

Methods: A systematic review of AK clinical guidelines was conducted. This informed the preparation of a three-round Delphi procedure followed by a consensus meeting, which combined the opinions of 16 clinical experts from 13 countries, to construct a structured consensus statement and a treatment algorithm positioning daylight photodynamic therapy (dl-PDT) among other AK treatment options.

Results: The systematic review found deficiencies in current guidelines with respect to new AK treatments such as ingenol mebutate and daylight photodynamic therapy. The Delphi panel established consensus statements across definition, diagnosis, classification and management of AK. While the diagnosis of AK essentially rests on the nature of lesions, treatment decisions are based on several clinical and non-clinical patient factors and diverse environmental attributes. Participants agreed on ranked treatment preferences for the management of AK, and on classifying AK in three clinical situations: isolated AK lesions requiring lesion-directed treatment; multiple lesions within a small field and multiple lesions within a large field, both requiring specific treatment approaches. Different AK treatment options were discussed for each clinical situation.

Conclusions: The results provide practical recommendations for the treatment of AK, which are readily transferable to clinical practice, and incorporate the physician's clinical judgement. The structured consensus statement positioned dl-PDT as a valuable option for patients with multiple AKs in small or large fields.

Introduction

Actinic keratosis (AK) is mainly caused by chronic ultraviolet (UV) radiation exposure, and is characterised by scaly or keratotic erythematous lesions.[1] Incidence increases with age and is highly dependent on individuals' geographical locations and skin types, as well as behaviours regarding sun exposure.[2] It is estimated that, in Australia, between 11% and 40% of white people older than 40 years have some form of AK.[3] Besides the cosmetic burden associated with AK, there is the risk that lesions, regardless of their clinical grade, will progress to squamous cell carcinoma (SCC).[4-6] With global ageing, AK will increasingly become a focus for healthcare systems.[7]

Although numerous scientific publications on AK exist, uncertainties remain regarding the definition of AK as pre-cancerous or *in situ* SCC and with respect to disease severity classification according to, for example, the Olsen grading system. Investigating these questions is among the aims of this study. The introduction of new treatments for AK has improved the standard of care for patients.[8] However, many guidelines place an emphasis exclusively on clinical efficacy and safety, without accounting for practical issues. These include considerations such as: the required treatment duration, adherence of patients to overly complex treatment regimens, compliance of frail patients to treatments with side effects (such as pain and time-to-healing), and uncertainty as to the exact lesion area to be treated.[9,10] These issues must be taken into account by treatment guidelines to ensure maximal compliance and adherence in a largely elderly patient population, and ultimately to maximise clinical efficacy in daily practice. Guidelines must also be updated to reflect current clinical practice; although recent treatments such as ingenol mebutate are included in global AK management guidelines, daylight photodynamic therapy (dl-PDT) is unclearly positioned in AK treatment guidelines.[11,12] **Error! Reference source not found.**Table

1 presents all AK treatments with their current approved clinical indications in the European Union. A practical and up-to-date consensus is necessary to further improve care in practice.

*>>**Table 1: EMA approval status of ranked treatments for AK**Error! Reference source not found.<<*

This study aimed to develop a structured consensus among clinical experts for the definition and management of AK. A systematic review of clinical guidelines for the management of AK was conducted, the output of which helped structure a Delphi panel. A consensus meeting comprising the same participants was organised to finalise consensus statements, as illustrated in Figure 1**Error! Reference source not found.**.

>>Error! Reference source not found.**Figure 1. Workflow summary of the consensus development<<**

Materials and Methods

For the systematic review, databases were searched for treatment guidelines and consensus statements for the management of AK, as shown in Table 2. Search terms for MEDLINE and EMBASE databases, respectively searched via Pubmed and Ovid are given in Appendix 1. Studies were critically assessed using the AGREE II-Global Rating Scale.[13] The AGREE II assessment tool allows evaluation of guideline methodology, including: guideline development methods, presentation, completeness of reporting, recommendation quality, and overall quality. The quality assessment is presented in Appendix 2. The search was conducted on September 4th 2015 and no limitations were applied in terms of publication dates; however, superseded versions of treatment guidelines were excluded.

>>Table 2. Systematic literature review methodology and search results<<

A Delphi panel was convened to outline a structured consensus among clinical experts on the definition and management of AK on the basis of the systematic literature review.

The Delphi technique is a research method aiming to rigorously organise convergence of opinion from participants concerning real-world issues.[14] It is an iterative process whereby a questionnaire is submitted in several rounds to selected experts. Each subsequent round is supported with a non-nominative qualitative summary of the previous round. Answers from participants are computed into a paragraph without mentioning which participants supported the statements to prevent clinical experts from influencing each other.[15] Summaries were associated with a consensus level ranging from 1 to 10 (where 1 corresponded to the lowest and 10 corresponded to the highest level of consensus) to inform participants on the level of consensus achieved in the previous round.

Questions relative to treatment preferences – treatments that participants considered to be the best for patients – and demographics, for which consensus was not sought, were submitted prior to the first Delphi round. These questions together constitute what is hereafter referred to as the one-off questionnaire; participants were asked to rank treatment options they considered most suitable for the management of isolated and multiple AK from a list of 16 options. Demographic questions included aspects relative to academic and medical contributions, and country of practice.

The Delphi panel consisted of three rounds. The Delphi questionnaire was developed by a scientific committee comprising three expert participants on the basis of the systematic review of guidelines. It focused on issues where lack of consensus was

identified, i.e. AK definition/diagnosis and factors influencing AK treatment decision-making. It also included a set of three clinical cases, represented in Figure 2**Error! Reference source not found.**, Figure 3**Error! Reference source not found.** and Figure 4**Error! Reference source not found.**, whereby participants were required to assess the nature of AK, list their preferred management options and express their view on the appropriateness of dl-PDT use. The latter question was included due to the absence of dl-PDT in existing guidelines, as demonstrated in the literature review.

>>Figure 2. Photograph representing clinical case 1<<

>>Figure 3. Photograph representing clinical case 2<<

>>Figure 4. Photograph representing clinical case 3<<

The one-off questionnaire and Delphi panel were communicated and collected via email, and included eight and 33 questions, respectively. Sixteen clinical experts were selected on the basis of their expertise on AK and their ability to constitute a worldwide panel, represented by: scientific contributions (peer-reviewed journal articles and conference keynotes), and/or clinical expertise in regards to high number of AK patients treated, and/or number of AK-related clinical trials they had participated in as investigator over the previous five years.

A list of treatment options for the management of AK was developed from the outputs of the Delphi panel and the systematic review of treatment guidelines. This was presented to the Delphi panel participants during a consensus meeting, and a final treatment algorithm was produced upon agreement of the expert panel.

Results

Systematic review of guidelines

Searches identified 612 citations for screening via database and hand searches, and nine treatment guidelines or consensus statements published between 2007 and 2015 were ultimately extracted (Table 2).[11,12,16-22] A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of the study flow is given in Appendix 3.

Where stated, all guidelines agreed that UV exposure was the most important causative factor for AK. Accordingly, high sun protection factor (SPF) sunscreen was recommended as a preventative measure in several guidelines.[11,16,18,22] Further UV-avoidance behaviours recommended by guidelines included: minimising peak-time exposure to the sun (11.00 am to 3.00 pm), wearing of broad-brimmed hats outdoors, and avoidance of artificial tanning.[11,22,23]

Within the reviewed guidelines, low consensus existed on the definition of the condition in terms of AK status as a cancer *in situ* or a pre-cancerous lesion. AK was described as a premalignant or pre-cancerous lesion in three guidelines.[16,17,22] Other guidelines regarded AK as either *in situ* SCC, or as a form of early-stage SCC.[12,18-21] Guidelines showed consensus in stating that a substantial risk exists for an AK lesion to progress to invasive SCC. Several guidelines produced guidance on grading AK severity. The Olsen grading system, or Röwbert-Huber classification, for AKs was used in some guidelines,[11,19] while others did not report specific guidance for assessing the severity of AK.[12,16,17,21,22]

A full summary of treatment recommendations across the guidelines is given in Appendix 4. For the medical and procedural management of isolated AK, the strongest recommendations made, by way of the frequency and strength of

recommendation, were for: cryotherapy, curettage and conventional photodynamic therapy (c-PDT). The weakest recommendations were made for 5-FU and imiquimod. Recommendations relating to curettage were found to be contradictory across guidelines, with guidelines applying a strong recommendation, weak recommendation, or no stated recommendation; as such, no consensus conclusion could be made from this evidence. For the management of multiple AK lesions, the strongest recommendations were made for c-PDT and 5-FU, then imiquimod and ingenol mebutate. The weakest recommendations were made for cryotherapy and laser therapies.[8,12,16-22] Results associated with cryotherapy are highly dependent on the physician's experience and skills, hence the recommendation variations for cryotherapy.

Critical assessment of the extracted guidelines was performed using the AGREE II guideline evaluation tool. Three guidelines scored perfectly [11,12,22] and there were no major methodological concerns for the remaining guidelines (see Appendix 2). However, reporting of strength of evidence was found to be incomplete in a minority of guidelines.[17,20] The recent introduction of ingenol mebutate, imiquimod 3.75%, 5-FU combined with salicylic acid, and dl-PDT also rendered all guidelines obsolete, as none fully reflected the full spectrum of currently-available treatments.[8] Additionally, some guidelines identified in this review provided recommendations restricted to specific geographical areas.[18,20] Some guidelines were also compromised by ignoring practicalities associated with treatment, including patient ability to comply with treatment, as well as the overall duration/complexity of the treatment cycle. Certain guidelines imposed an overly theoretical approach to treatment, such as proposing AK maximal treatable area thresholds of 25 cm^2, which is not a realistic threshold in clinical practice as a cheek and forehead represent 100 to 150 cm^2 and a bald scalp

extends over 200 cm^2.[17,18] Some guidelines also advised four-week treatment courses (e.g. 5-FU, 3.75% imiquimod),[8] with likely physician follow-up visits afterwards: a prolonged treatment period which would likely prove difficult for some patients.[11,12,16-22] Finally, specific management for immunosuppressed patients was not addressed in some treatment guidelines.[16,22]

One-off questionnaire and Delphi panel

Sixteen clinical experts with extensive experience on AK participated in the Delphi panel. Over the past five years, participants reported a median of, 75 AK patients seen on a monthly basis, 11 AK-related publications, 25 AK-related conference keynotes and four AK-related clinical trials where acting as research investigator, as detailed in Table 3.

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Table 3. Descriptive characteristics of actinic keratosis participating clinical experts<<

Definition, diagnosis and grading of AK. A consensus could not be found on the definition of AK as either cancer *in situ* or pre-cancerous lesions throughout the two initial rounds of the Delphi panel (data not shown). A statement relative to the existence of a disease continuum from AK to invasive SCC led to a consensus.

Table 4 displays consensus statements relative to the definition and diagnosis of AK. Although reservations were expressed regarding its optimality, participants agreed that the Olsen grading system was useful in clinical practice. On the clinical relevance of the number, size, and thickness of AK lesions, participants generally agreed that these were crucial criteria for evaluating the severity of AK, and agreed that the distribution of AK lesions was not an important factor when establishing a diagnosis.

Experts agreed that it is essential to distinguish isolated AK lesions from those occurring in small and large fields of actinic damage, in order to make appropriate treatment decisions. Although stating that it was an arbitrary figure participants reached the consensus that five AK lesions is an appropriate threshold to distinguish isolated AK (<5 lesions) from multiple AK (≥5 lesions) within a small field. Several treatments for AK are only indicated for the treatment of isolated lesions, small fields of actinic damage, and some others for large fields of actinic damage, as shown in Table 1**Error! Reference source not found.**. The site of lesions was considered to be of moderate relevance for the diagnosis of AK. Participants agreed that patients with multiple AK always display a field of actinic damage surrounding the lesions.

>>Table 4. Summary of consensus statements relative to the diagnosis of AK<<

Management of AK. Participants agreed that decisions for the treatment of AK were based on multiple attributes, namely: patient clinical and non-clinical factors, healthcare, environmental, and economic factors. Table 5 and Table 6 display the consensus statements relative to these factors and attributes upon which participants agreed.

Although participants agreed that the diagnosis of AK is based on a clinical assessment, they agreed on the necessity to conduct biopsies for suspicious lesions, meaning any of (but not exclusive to): infiltrated, painful, inflamed, and/or hyperkeratotic. Efficacy of treatments was identified as a paramount factor influencing treatment decisions, regardless of the patient's immunosuppression status.

Participants also agreed that while age was not an important attribute for treatment decision-making, concern was raised regarding patient capacity to comply with self-administered treatments when physical function is impaired. Achieving optimal

compliance, and therefore best treatment outcomes, should be among the main drivers of treatment decisions, in alignment with patients' physical and mental capacity.

Similar to patient-level economic capability and technology availability, specific attributes of healthcare systems influence treatment decisions across the world. This is due to varying healthcare situations and treatment/technology availability in standard practice across different countries.

Participants agreed that the main motivation for physicians to initiate treatment for AK is the prevention of lesion progression to invasive SCC; it was considered that patients, although also concerned with cancer, have a strong preference for treating aesthetic and comfort impairments when seeking treatment for AK.

As immunosuppressed patients are at greater risk of progression to invasive SCC, a consensus was determined on the necessity for immediate primary preventive measures and curative treatments.

>> Table 5. Summary of lesion and patient factors influencing AK treatment decision <<

>> Table 6. Attributes influencing AK treatment decision and motivations for treatment initiation <<

Resulting from the one-off questionnaire, the preferred management option for the treatment of isolated AK lesions was cryotherapy with an average of rank 1 – although acknowledging the crucial influence of the physician's ability and experience – followed by imiquimod and the newest combination of 5-fluorouracil (5FU) with salicylic acid (average rank of 4). The preferred treatment for multiple AK lesions was dl-PDT (average rank of 1). Ingenol mebutate and c-PDT were the next most-preferred treatments (average rank of 2 for both).

>> Table 7. Participants' average ranking of preferred treatments of isolated and multiple AK (results from the one-off questionnaire) <<

The three clinical cases shown in Figure 2, Figure 3 and Figure 4 represent *a priori* a spectrum of AK severity with varying lesion thickness, i.e. respectively isolated lesions, multiple lesions in limited areas, and multiple lesions in large fields of actinic damage. Expert perception of clinical assessments, management decisions and appropriateness of treatment options, including dl-PDT for clinical cases 1, 2 and 3 are reported in Table 8, which presents summaries alongside the consensus level from the third round of the Delphi panel.

Participants ultimately established that clinical case 1 displayed isolated AK, grade I/II with uncertainty regarding field cancerisation. The participants' preferred treatment was cryotherapy, with recognised risk of hypopigmentation being a practical issue.

Consensus was found to describe clinical case 2 as multiple AK, grades I, II and III in an area of field cancerisation. Participants agreed on the need to consider biopsy for the thicker lesion and field preparation to remove hyperkeratosis before field treatment, after which c-PDT would be preferred, followed by dl-PDT or 5-FU. Here, dl-PDT was considered appropriate for the treatment of the thinner lesions.

Participants agreed that clinical case 3 displayed multiple AK lesions, grades I/II and an area of field cancerisation. Field treatment would be required, with a participants preferring using dl-PDT, followed by c-PDT, imiquimod and 5-FU.

>> Table 8. Findings for the assessment, treatment and use of daylight PDT for clinical cases 1, 2 and 3 <<

List of treatment options

Figure 5**Error! Reference source not found.** shows the list of treatment options finalised at the consensus meeting of panel participants. Considering the number of significant factors and attributes influencing treatment decisions including clinical data, efficacy, safety, tolerability, labels, and clinical experience, different treatment options were considered for the different clinical situations. For example, dl-PDT was rated as a preferred option for patients with multiple AK on both small and large fields due to its efficacy and tolerability profile. Ingenol mebutate was rated as a valuable option for isolated AK lesions and multiple AK lesions on small fields due to its surface limitation per label, as well as its tolerability profile. Imiquimod 5% was rated as valuable option for the same profiles due to its tolerability profile, whereas Imiquimod 3.75% was rated as valuable option for multiple AK on large field as per its label. This Delphi panel therefore provides an outline of treatment factors to consider when physicians assess their own clinical cases.

On the basis of management preferences expressed by participants, a distinction was made for the management of multiple lesions and fields of actinic damage, which were further divided between small and large fields of actinic damage. Although intentionally left ill defined, as the limitation of 25cm^2 for some approved treatments is not realistic in clinical practice, the distinction between small and large fields of actinic damage allows treatment of restricted zones (e.g. nose, one cheek or part of forehead) or entire body areas (e.g. full scalp or full face). It was also decided to include specific recommendations for immunocompromised patients on the basis of the Delphi panel findings and further discussions during the consensus meeting.

*>>Error! Reference source not found.****Figure 5. Treatment algorithm for the management of actinic keratosis****<<*

Discussion

This study reports the findings of a systematic review of clinical guidelines for AK, and how the results have been used, in conjunction with an evolving consensus among clinical experts, to develop both consensus statements and a treatment algorithm. The treatment algorithm accounts for recent treatments and reflects on the limitations of past guidelines. Participants agreed on a treatment algorithm for the management of isolated and multiple AK, distinguishing lesion-directed treatment, small and large fields of actinic damage. Participants to the panel have agreed that isolated lesions should be removed with lesion directed treatments whereas multiple lesions should be treated differently if they spread over small or large fields. This is due to some treatment being approved only for smaller areas. Treating larger surfaces with treatments approved for smaller areas would require the physician to repeat consecutive cycles on adjacent areas, which can lead to an unacceptable overall treatment duration, increase the extent of treatment side effects and incur a strong increase of direct and indirect costs. This study reflects current preferences of experts on management of AK and reports dl-PDT, c-PDT, ingenol mebutate and imiquimod as preferred field treatments. This study's outcome is also supported by recent findings showing that dl-PDT has a superior tolerability profile and is more cosmetically acceptable and preferred by patients [24]. Considerations were made when detailing attributes and factors influencing treatment decision-making, ranging from the patient's characteristics of AK lesions to the availability of technologies in practice.

In addition, clinical experts with extensive experience of AK management have highlighted a number of practical issues to be considered when treating AK. The

consensus recommendations made are current and easily translatable to clinical practice.

The current study is a structured consensus, and should not be considered a treatment guideline. This avoids the rigidity and limitations of guidelines, while providing methodologically aggregated opinions of worldwide renowned experts in the field of AK. Importantly, the consensus statement offers practical recommendations, allowing physicians to use their clinical judgement on each patient case. Furthermore, considering the limited long-term experience and knowledge on AK, a structured consensus rests among the most useful available evidence for treatment decisions at this point.

Tables

Table 1: EMA approval status of ranked treatments for AK

Treatment	Indication
c-PDT/dl-PDT MAL (Metvix®)[25]	Treatment of thin or non-hyperkeratotic and non-pigmented AK on the face and scalp when other therapies are considered less appropriate.
Imiquimod 3.75% (Zyclara®)[26]	Clinically typical, non-hyperkeratotic, non-hypertrophic, visible or palpable AK of the full face or balding scalp in immunocompetent adults when other topical treatment options are contraindicated or less appropriate.
Imiquimod 5% (Aldara®)[27]	Clinically typical, non-hyperkeratotic, non-hypertrophic AK on the face or scalp in immunocompetent adult patients when size or number of lesions limit the efficacy and/or acceptability of cryotherapy and other topical treatment options are contraindicated or less appropriate.
Ingenol mebutate (Picato®)[28]	Ingenol mebutate is indicated for the cutaneous treatment of non-hyperkeratotic, non-hypertrophic actinic keratosis in adults. The content of one tube should be used for one treatment area of 25 cm^2.
5-FU + salicylic acid	Treatment of AK. Response can be seen as early as in six weeks. Response increases over time and data are available for treatment up to 12 weeks. Complete healing of the

(Actikerall®)[29]	lesion(s) or optimal therapeutic effect may not be evident for up to eight weeks after treatment cessation.
5-FU (topical) (Efudix®)[30]	Treatment of AK. The cream should be applied thinly to the affected area once or twice daily; an occlusive dressing is not essential.
Diclofenac/ hyaluronate (Solaraze®)[31]	Treatment of AK. The amount needed depends on the size of the lesion. Usual duration of therapy: 60 to 90 days. Maximum efficacy has been observed with treatment duration towards the upper end of this range. Complete healing of the lesion(s) or optimal therapeutic effect may not be evident for up to 30 days following cessation of therapy. Long term efficacy not established.
c-PDT ALA (Ameluz®)[32]	Treatment of AK of mild to moderate intensity on the face and scalp (Olsen grade 1 to 2)

AK: actinic keratosis; c-PDT: conventional photodynamic therapy; dl-PDT: daylight photodynamic therapy; MAL: Methyl aminolevulinate; ALA: 5-aminolaevulinic acid

Table 2. Systematic literature review methodology and search results

Search details	
Databases searched	MEDLINE MEDLINE-in-Process EMBASE
Limits	Population: Patients with AK Intervention: No restriction Comparator: No restriction Outcomes: Multi-treatment recommendations for management of actinic keratosis Study Type: Clinical guidelines from recognised large organisations, consensus statements
Hand searches	Dermatology organisations, relevant conference abstracts/posters (from 2012)
Inclusion criteria	Conference abstracts of interest: published 2012 – 2015 Study type of interest: Treatment guideline or recommendation Population of interest: Patients with AK Outcome of interest: Recommendations for the management of AK Locations of interest: EU, Latin America,

	Australia, Canada
Exclusion criteria	Duplicate, not in the language of interest (English), abstract that is reported elsewhere
Search results	
Number of references identified through the systematic literature searches	n = 609
Number of references identified through the hand searches	n = 3
Number of articles included in the systematic review	n = 9

Table 3. Descriptive characteristics of actinic keratosis participating clinical experts

Countries of practice	Two each from: Germany, Italy, Canada One each from: France, Netherlands, Denmark, UK, Spain, Greece, Mexico, Brazil, Argentina, Australia
Average monthly number of AK patients seen (range (median))	20-400 (75)
Number of AK-related peer-reviewed journal articles in the last 5 years (range (median))	0-22 (11)
Number of AK-related conference keynotes in the last 5 years (range (median))	0-50 (25)
Number of AK-related clinical trials where acting as investigator in the last 5 years (range (median))	0-20 (4)

AK: actinic keratosis; UK: United Kingdom

Table 4. Summary of consensus statements relative to the diagnosis of AK

Legend: computed summaries of the third iteration of the Delphi panel on questions relative to the diagnosis of AK.

Topic	Consensus statement
AK: cancer *in situ* or pre-cancerous lesions?	Regardless of lesion thickness, there is a disease continuum extending from AK to invasive SCC.
Olsen grading: appropriate for AK diagnosis?	Although it could be improved, the Olsen grading system is appropriate mainly because it is currently a standard used in practice and in clinical trials for diagnosis and prognosis. It is a useful tool in clinical practice. Using a thin/thick grading system may also be useful.
Number of lesions differentiate isolated and multiple AK	Although it is an arbitrary threshold, isolated AK is represented by less than five AK lesions, while multiple AK is represented by five AK lesions or more. This threshold is not fixed and other factors such as the size of the AKs and surrounding skin photo damage may modify the diagnosis. The number of lesions is of paramount importance to clinically describe the severity of AK. It is the number one criterion to assess the severity of AK. However, it is not the only criterion and needs to be combined with lesion size and thickness.

Lesion size and thickness	The thickness of lesions is at least as important as the number of lesions for diagnosis. The size of lesions is a crucial criterion for the clinical definition of AK, although of less importance than the number of lesions.
Surrounding skin and field of actinic damage	In a patient with multiple AK, it is very likely that surrounding skin harbours a field of actinic damage as a similar sun exposure has been sustained.
Lesion distribution	The distribution of lesions as a characteristic for the clinical assessment of AK is moderately relevant to AK diagnosis.

AK, actinic keratosis; SCC, squamous cell carcinoma.

Table 5. Summary of lesion and patient factors influencing AK treatment decision.

Legend: computed summaries of the third iteration of the Delphi panel on questions relative to patient factors influencing AK treatment decisions.

Topic	Consensus statement
Lesion nature	Lesion number and thickness are the most important criteria (see previous table). The size of lesions is also to be considered for treatment decision. Thicker and/or larger lesions may require a biopsy and prior intervention before treatment initiation and more careful follow-up. Treatment of the surrounding actinic damage may be necessary. Lesion distribution can be important when choosing treatments: hard to reach locations for application may require the help of caregivers.
Immunosuppression status	The immunosuppression status of a patient strongly influences treatment decisions. It influences other AK characteristics such as the number and invasiveness potential of lesions. Immunosuppressed patients must be managed more carefully as they are at greater risk of invasive SCC: treatment choices are different as treatment safety and efficacy vary and knowledge is sometimes scarce in this population subgroup. Sun protection is key to prevent new lesions in immunosuppressed patients.

Patient treatment history	Patient's treatment history and their treatment preferences are important attributes for treatment decision-making, to ensure maximal adherence and optimal treatment outcomes.
Other patient clinical attributes	Several other attributes influence treatment decisions, including time to healing; patient's AK/SCC history plays a role in management decisions
Patient characteristics	Patient's age is generally not an important attribute in treatment decisions. However, the patient's capacity to comply with treatments matters. This includes health aspects such as the understanding of the treatment modality, the manual ability to manage treatments by him/her-self and dependency or presence of family or professional caregivers. Although this can never be taken for granted, older people have a lesser focus on cosmetic aspects of the condition. This patient preference may influence treatment choices. The relevance of patients' economic status as an attribute for prescribing specific treatments varies according to countries' healthcare settings.

PDT, photodynamic therapy; AK, actinic keratosis; SCC, squamous cell carcinoma.

Table 6. Attributes influencing AK treatment decision and motivations for treatment initiation

Legend: computed summaries of the third iteration of the Delphi panel on questions relative to attributes not related to patients influencing treatment decisions and motivations for treatment initiation.

Topic	Consensus statement
Time	Time is an important attribute for treatment choices. Doctors seek optimal patient treatment compliance. Hence, treatment duration and regimen do influence treatment decisions.
Medical results	The importance of medical results in treatment choices is paramount, firstly regarding efficacy but also safety. The existence (or absence) of high quality scientific evidence also drives treatment choices.
Availability of technology	The availability of technologies only influences treatment decisions in settings where not all devices/treatments are available.
Economic attributes	Economic attributes have a significant impact on prescribing. Treatments are not always reimbursed, either by private or public insurance. Some treatments are not approved for AK III. Costs to the healthcare system rarely influence prescribing decisions. In some settings hospitalisation is a way to gain healthcare coverage for certain treatments. As an example, requirements for daylight exposure with dl-

	PDT introduce a seasonal and geographic component in some markets, which influences treatment decisions.
Motivations for treatment initiation	The main motivation of doctors to treat AK is the prevention of the progress of lesions to SCC. Patient motivations for initiating AK treatment mainly include (order varies) aesthetics, pain/discomfort and fear of developing/having skin cancer.

AK, actinic keratosis; PDT: photodynamic therapy; dl-PDT: daylight photodynamic therapy; SCC, squamous cell carcinoma.

Table 7. Participants' average ranking of preferred treatments of isolated and multiple AK (results from the one-off questionnaire)

Legend: Average ranking for each management option for isolated and multiple AK provided by participants in the one-off questionnaire. Exact question asked: 'In your practice, can you rank treatments for isolated/multiple AK that you consider to be the best for your patients (best (1) to worst (16))? You may use the same number several times if you wish.'

Isolated lesions[1]		**Multiple lesions**[1]	
Cryotherapy	1	Dl-PDT	1
Imiquimod[2]	4	Ingenol mebutate	2
5-FU + salicylic acid.	4	C-PDT	2
5-FU	5	Imiquimod[2]	3
Ingenol mebutate	5	5-FU	3
Curettage	5	Diclofenac/hyaluronate (top.)	6
C-PDT	5	5-FU + salicylic acid.	8
Dl-PDT	6	Laser resurfacing	9
Excision	9	Cryotherapy	10
Diclofenac/hyaluronate (top.)	10	Chemical peels	10
Ablative CO_2 laser	11	Curettage	11
Surveillance	13	Dermabrasion	11

Dermabrasion	15	Excision	15
Chemical peels	15	Surveillance	15
DNA repair enzymes	15	Nothing	16
Nothing	16	DNA repair enzymes	16

5-FU: 5-fluorouracil; top.: topical; c-PDT: conventional photodynamic therapy; dl-PDT: daylight photodynamic therapy.

[1] In the early stages, the study did not consider small or large fields of actinic damage.

[2] In the early stages of the study, imiquimod 5% and 3.75% were not differentiated.

Table 8. Findings for the assessment, treatment and use of daylight PDT for clinical cases 1, 2 and 3

Legend: Results from each of the three iterations of the Delphi panel relative to the assessment, treatment preferences and appropriateness of use of dl-PDT for clinical case 1, 2 and 3. Exact questions asked: 'The following three questions are clinical cases. On the basis of the following pictures, please assess the clinical features of AK and the most appropriate treatment to provide. Please assume that patients are not immunocompromised. (1) Clinical assessment of clinical case 1/2/3. (2) What are the most appropriate treatments for clinical case 1/2/3? (3) Is daylight PDT relevant for clinical case 1/2/3?'

	Assessment	**Treatment**	**Dl-PDT use**
Clinical case 1 – round 3	Isolated AK, grades I/II with uncertainty regarding field cancerisation. (CL: 10)	Although there is a risk of hypopigmentation, cryotherapy is among the first treatment options. Then (order varies) c-PDT, imiquimod or 5-FU, ingenol mebutate (CL: 8)	Dl-PDT (most often to the whole face) is more appropriate when multiple AK and/or suspecting a cancerisation field. In the case of single lesions, more practical alternatives are preferable. Reimbursement status may affect the use of dl-PDT. (CL: 9)

Clinical case 2 – round 3	Multiple AK grades I, II and III in an area of field cancerisation. (CL: 10)	Biopsy is considered for thick lesions. Prior to treatment, field preparation using curettage is required. First option for treatment is c-PDT, then (order varies) dl-PDT, or 5-FU. Last Imiquimod and Ingenol Mebutate may be used. (CL: 9)	Dl-PDT is appropriate for the thinner lesions. Thicker lesions must be treated separately and prior to dl-PDT. (CL: 10)
Clinical case 3 – round 3	Multiple AK, Grade I/II and field cancerisation. (CL: 10)	Field treatment is required, with preferably dl-PDT but also c-PDT, Imiquimod, 5-FU. (CL: 9)	Yes. This choice may depend on dl-PDT reimbursement status and sun exposure (season/location). (CL: 10)

c-PDT: conventional photodynamic therapy; dl-PDT: daylight photodynamic therapy; AK, actinic keratosis; CL: consensus level; 5-FU: 5-fluorouracil.

Figures

Figure 1. Workflow summary of the consensus development

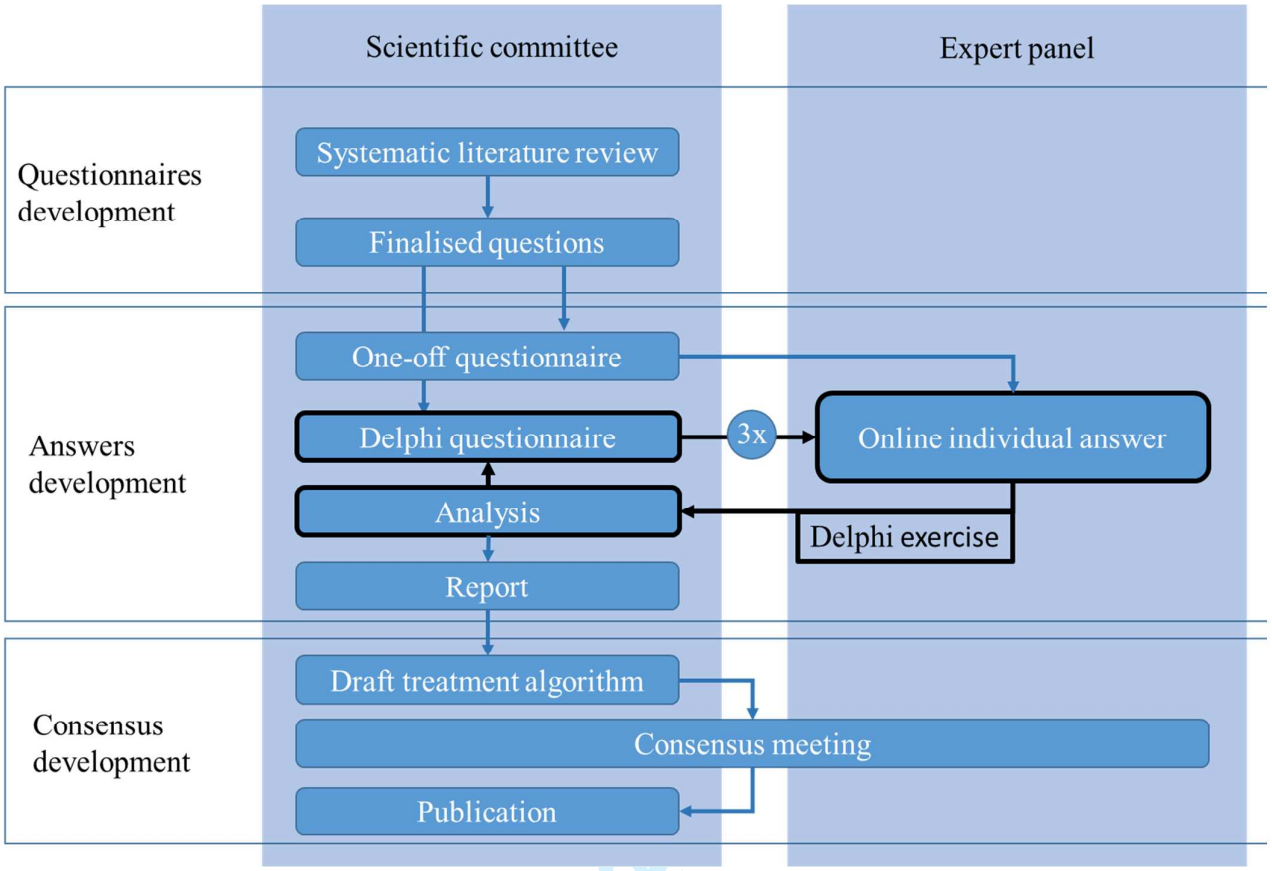
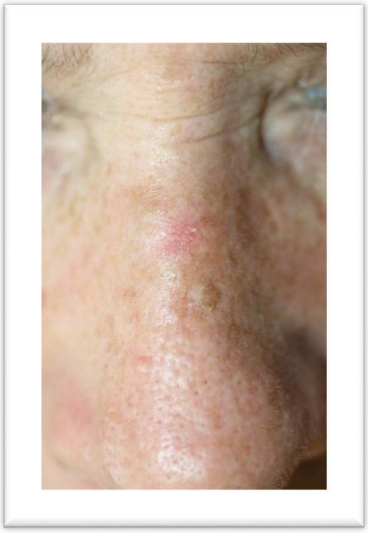
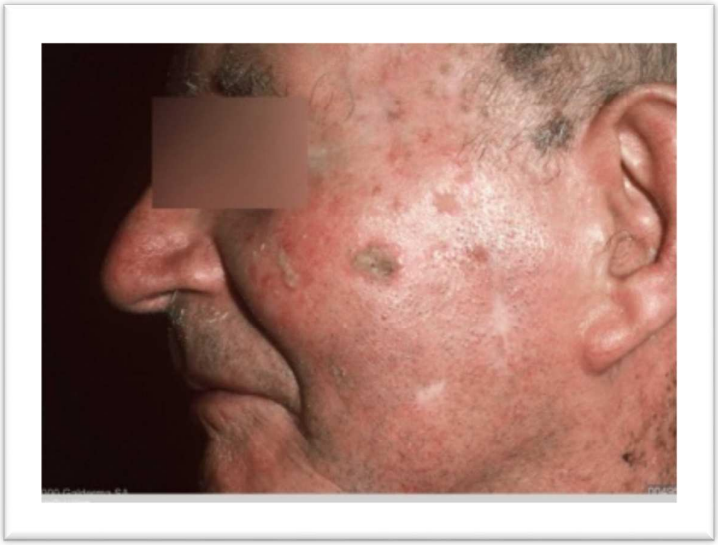


Figure 2. Photograph representing clinical case 1



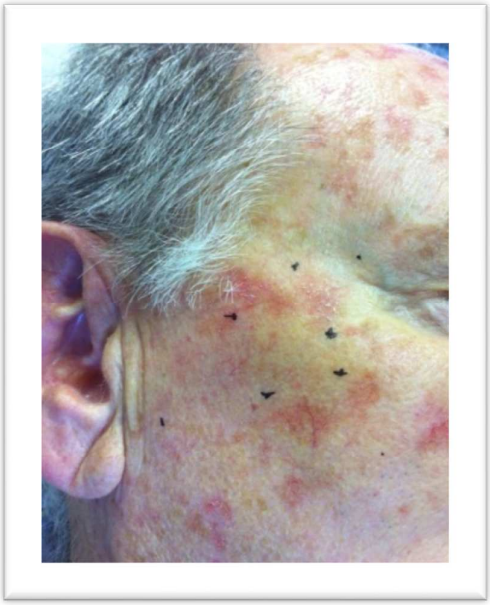
Source: DermQuest.com

Figure 3. Photograph representing clinical case 2



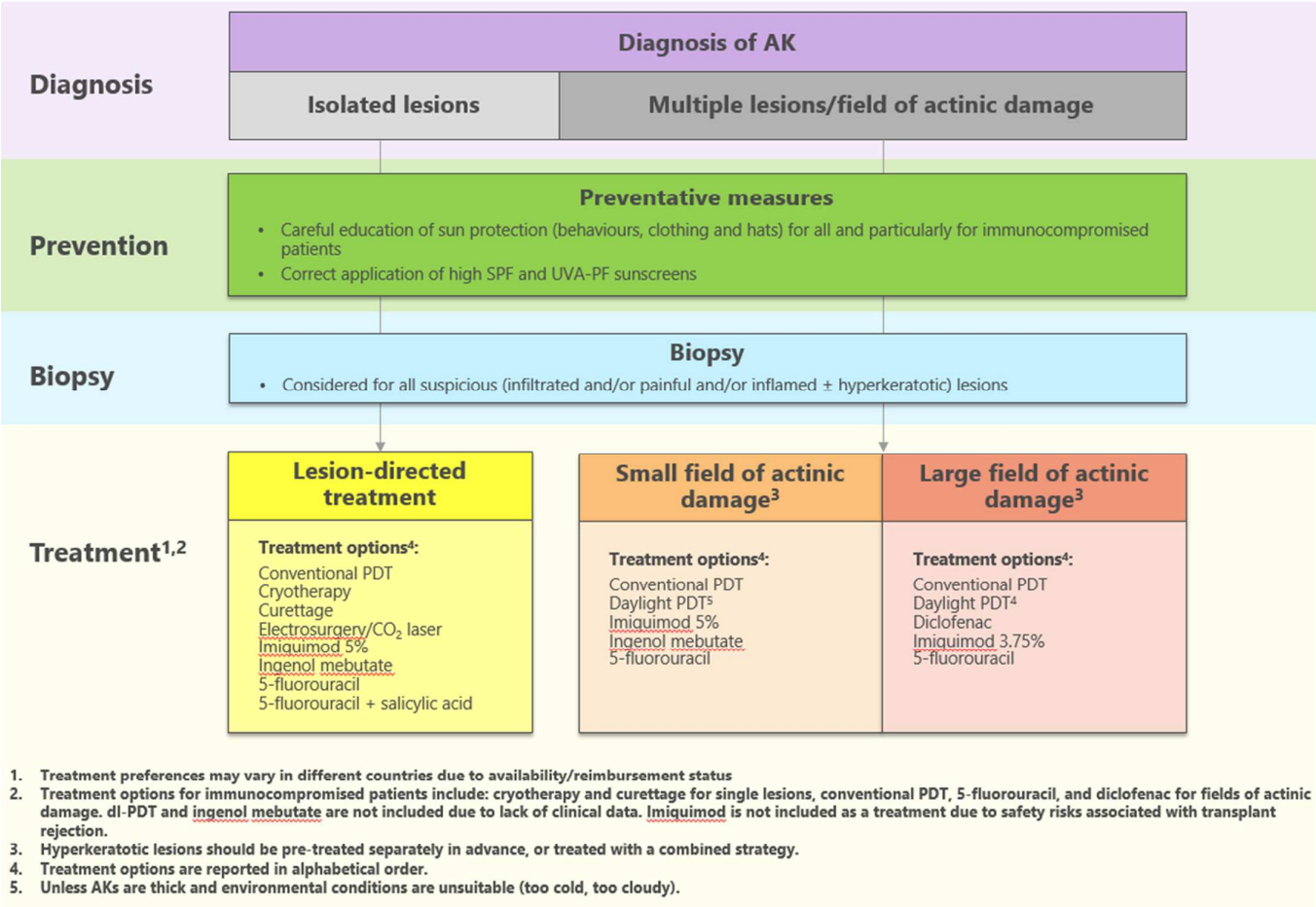
Source: DermQuest.com

Figure 4. Photograph representing clinical case 3



Source: Department of Dermatology, University of Brescia, Brescia, Italy

Figure 5. Treatment algorithm for the management of actinic keratosis



PDT, photodynamic therapy; AK, actinic keratosis.

Appendix 1: Search terms for the systematic review of clinical guidelines

MEDLINE and MEDLINE-in-Process via Pubmed

#	Search terms
1	keratosis, actinic[mh] OR (actinic[tiab] AND keratos*[tiab]) OR (Solar[tiab] AND keratos*[tiab]) OR (senile[TIAB] AND keratos*[TIAB]) OR hyperkeratos*[TIAB]
2	guideline[PT]
3	Clinical pathway[mh] OR Clinical protocol[mh] OR Consensus[mh] OR Consensus development conferences as topic[mh]
4	Critical pathways[mh] OR Guidelines as topic [Mesh:NoExp] OR Practice guidelines as topic[mh] OR Health planning guidelines[mh] OR guideline[pt] OR practice guideline[pt]
5	consensus development conference[pt] OR consensus development conference, NIH[pt] OR position statement*[tiab] OR policy statement*[tiab]
6	practice parameter*[tiab] OR best practice*[tiab] OR standards[ti] OR guideline[ti] OR guidelines[ti] OR ((practice[tiab] OR treatment*[tiab]) AND guideline*[tiab])
7	CPG[tiab] OR CPGs[tiab] OR consensus*[tiab] OR ((critical[tiab] OR clinical[tiab] OR practice[tiab]) AND (path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR protocol*[tiab]))
8	recommendat*[ti] OR (care[tiab] AND (standard[tiab] OR path[tiab] OR paths[tiab] OR pathway[tiab] OR pathways[tiab] OR map[tiab] OR maps[tiab] OR plan[tiab] OR plans[tiab]))
9	(algorithm*[tiab] AND (screening[tiab] OR examination[tiab] OR test[tiab] OR tested[tiab] OR testing[tiab] OR assessment*[tiab] OR diagnosis[tiab] OR diagnoses[tiab] OR diagnosed[tiab] OR diagnosing[tiab])) OR (algorithm*[tiab] AND (pharmacotherap*[tiab] OR chemotherap*[tiab] OR chemotreatment*[tiab] OR therap*[tiab] OR treatment*[tiab] OR intervention*[tiab]))
10	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11	#1 AND #10

EMBASE via Ovid

#	Search terms
1	actinic keratos$.mp. or exp Keratosis, Actinic/ OR solar keratos$.mp. OR senile keratos$.mp. OR hyperkeratos$.mp
2	exp clinical pathway/
3	exp clinical protocol/
4	exp consensus/
5	exp consensus development conference/
6	exp consensus development conferences as topic/
7	critical pathways/
8	exp guidelines/
9	guidelines as topic/
10	exp practice guideline/

11	practice guidelines as topic/
12	health planning guidelines/
13	treatment guidelines.mp.
14	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
15	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab.
16	(standards or guideline or guidelines).ti.
17	((practice or treatment*) adj guideline*).ab.
18	(CPG or CPGs).ti.
19	consensus*.ti.
20	consensus*.ab. /freq=2
21	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab.
22	recommendat*.ti.
23	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab.
24	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab.
25	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab.
26	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 Or #20 OR #21 OR #22 OR #23 OR #24 OR #25
27	#1 AND #26

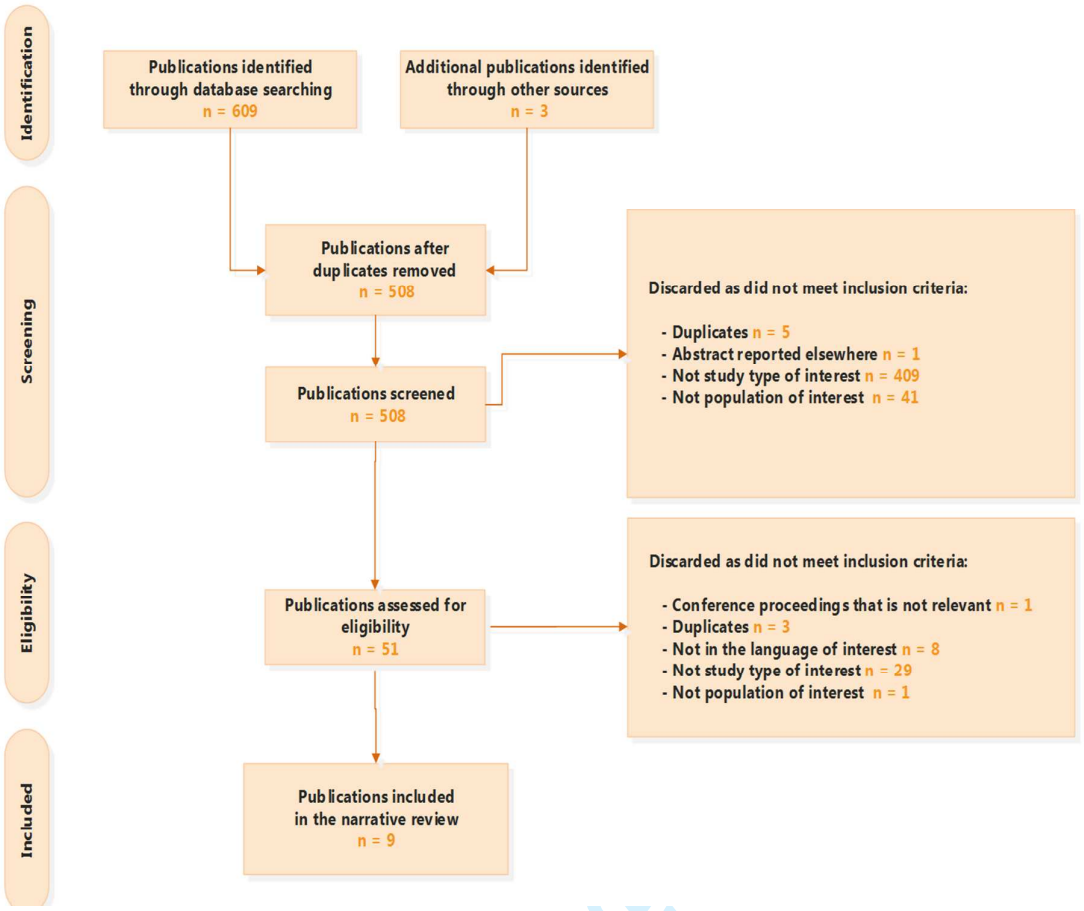
Appendix 2: Quality assessment – AGREE II-Global Rating Scale

Title	Author(s)	Rate the overall quality of the guideline development methods	Rate the overall quality of the guideline presentation	Rate the completeness of reporting.	Rate the overall quality of the guideline recommendations	Rate the overall quality of the guideline
Guidelines for the management of actinic keratoses	De Berker et al.	7	7	6	6	6
Management of actinic keratosis: a practical report and treatment algorithm from AKTeam expert clinicians	Dreno B.;Amici J et al.	6	6	7	7	6
Spanish adaptation of the European guidelines for the evaluation and treatment of actinic keratosis	Ferrándiz C et al.	4	7	7	7	7
Swiss clinical practice guidelines on field cancerization of the skin	Hofbauer G et al.	6	6	7	7	6
Key Opinion Leader (KOL) consensus for	Peserico A	4	6	5	4	5

Title	Author(s)	Rate the overall quality of the guideline development methods	Rate the overall quality of the guideline presentation	Rate the completeness of reporting.	Rate the overall quality of the guideline recommendations	Rate the overall quality of the guideline
actinic keratosis management in Italy: The AKTUAL Workshop	et al.					
Development of a treatment algorithm for actinic keratoses: A European Consensus	Stockfleth E et al.	6	7	7	7	7
Guidelines for the diagnosis and treatment of cutaneous squamous cell carcinoma and precursor lesions	J.J. Bonerandi et al.	7	7	7	7	7
Non-melanoma Skin Cancer in Canada Chapter 3: Management of Actinic Keratoses	Poulin Y et al.	7	7	7	7	7
Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis	R.N. Werner et al.	7	7	7	7	7

Quality is rated from 1 (worst) to 7 (best)

Appendix 3: PRISMA diagram for systematic review of clinical guidelines



Appendix 4: Summary of recommendations for the management of actinic keratosis

Legend: Table representing recommendations for the management of AK as reported in publications included in the systematic review of clinical guidelines.

	No therapy	Emollient	Salicylic acid	5-FU	Diclofenac	Imiquimod 5%	Ingenol mebutate	Topical retinoids	Systemic retinoids
De Berker 2006[a]	A, II-ii	A, I	A, III	A, I	B, I	B, I			
Dreno 2014[b]			1st line	1st line	1st line	1st line	1st line		
Ferrándiz 2014[c]			2 (with 5-FU)	2	2	2	2		3
Hofbauer 2014[d]				FD, 1	FD, 1	FD, 1	FD, 1	FD, 2	
Peserico 2013[e]	Sunblock: 0.0[1], 0.0[2]				1.21 2.22	1.71 2.72			
Stockfleth 2008[f]				50%	50-79%	55-84%			0-85%
Bonerandi 2011[g]				1, LOE1		1, LOE1			
Poulin 2015[h]				S: Weak (mod.) M: Weak (low)		S: Strong (high) M: Strong (high)	S: Strong (high) M: Strong (high)		
Werner 2015[i]			S: ↑ (with 5-FU)	S: ↑ M: ↑↑	S: 0 M: ↑	S: ↑ M: ↑↑ (imiquimod 3.75%)	M: ↑↑		

	PDT	Cryosurgery	Curettage	Excision	Laser	Chemical peeling	Dermabrasion	Radiotherapy
De Berker 2006[a]	B, I	A, I			C, III	C, III	C, III	
Dreno 2014[b]	1st line	1st/2nd line	1st/2nd line		1st line		1st line	
Ferrándiz 2014[c]	2	1	1		1 (CO_2)	3	3	
Hofbauer 2014[d]	FD/LD, 3 (ALA, MAL)		LD, 4	LD (N/A)	FD, 3	FD, 3	FD, 4	FD, 4
Peserico 2013[e]	2.8[1], 4.8[2]	3.8[1], 1.7[2]	0.5[1], 0.3[2]	3.2[1], 1.0[2]	CO_2: 3.0[1], 1.3[2] Erbium: 0.3[1], 1.0[2]	0.5[1], 0.2[2]		
Stockfleth 2008[f]	70-90% #	75-98%	Undocumented	Undocumented	~90%	~75%		
Bonerandi 2011[g]	1, LOE2	1						
Poulin 2015[h]	M: Strong (high)	S: Strong (mod.)	S: Strong (mod.)	S: Strong (mod.)	M: Low (weak)	M: Low (weak)		
Werner 2015[i]	S: ↑ M: ↑↑	S: ↑↑ M: ↑	S: ↑ M: 0		S: 0 M: ↑			

[a] Strength of recommendation rated from A (best) to E (worst) and quality of evidence rated from I (best) to IV (worst)

[b] Therapies recommended for: 1: first line treatment for non-hyperkeratotic or hyperkeratotic isolated/multiple AK, or 1*: first line treatment of isolated/small numbers of AK and second line treatment in cases of recurrence

[c] Recommendations were made according to the following treatment aims: 1: Destructive therapies should be applied to solitary AKs or whenever invasive SCC is suspected. 2: Topical treatments are preferable to destructive ones in patients with multiple AKs or evident field

cancerization because topical formulations treat both the visible lesions and the field. 3: Orally administered systemic retinoids, dermabrasion, chemical peelings, and CO_2 laser treatments are second-line or coadjutant therapies. They should be considered for use in special circumstances.

[d] Therapies recommended for lesion-directed (LD) or field-directed (FD) treatment. Level of evidence reported according to OCEBM

[e] Treatment options for [1]: isolated AK, or [2]: multiple AK/filed cancerisation, were ranked according to consensus (1 = completely disagreed - 5 = completely agreed)

[f] Treatments were evaluated according to response rate, #: response rates enhanced by curettage

[g] First-line therapies for isolated/multiple AK are presented

[h] Strength of recommendation (and level of evidence) given for single (S) or multiple (M) AKs

[i] Recommendations for single (S) or multiple (M) AKs. ↑↑: Strong recommendation; ↑: Weak recommendation; 0: No recommendation

AK: Actinic keratosis; FD: Field-directed; LD: Lesion-directed; LOE: Level of evidence; OCEBM: Oxford Centre for Evidence Based Medicine; M: Multiple AK; Mod.: Moderate; S: Single AK; SCC: Squamous cell carcinoma

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Nil

Declaration of conflict of interest

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