Evidence and consensus based (S3) Guidelines for the Treatment of Actinic Keratosis

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International League of Dermatological Societies (ILDS) in cooperation with the European Dermatology Forum (EDF)

Long Version (online supplement)

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Abbreviations

5-FU	5-fluorouracil
AE	adverse events
AK, AKs	actinic keratosis, actinic keratoses
ALA-PDT	5-aminolevulinic acid-photodynamic therapy
CC	complete clearance
CI	confidence interval
EADV	European Academy of Dermatology and Venereology
EDF	European Dermatology Forum
GP	general practitioner(s)
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HA	hyaluronic acid
IGII	Investigator global improvement index
ILDS	International League of Dermatological Societies
MAL-PDT	methylaminolevulinate-photodynamic therapy
NMSC	Non melanoma skin cancer
PC	partial clearance
PGII	participant global improvement index
RR	relative risk
SA	salicylic acid
SCC	squamous cell cancer of the skin
SoF table	summary of findings table
UEMS	European Union Of Medical Specialists
UV, UVR	ultraviolet, ultraviolet radiation

List of tables

1. Introduction

Nast / Werner

This document is the long version (online supplement) of the

Evidence and consensus based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies (ILDS) in cooperation with the European Dermatology Forum (EDF).

In this document, no detailed description of the guidelines development process is provided. A detailed description of the guidelines development process and a more comprehensive description of the results of the systematic assessment of interventions is available in the methods and results report of the guidelines (available at JEADV DOI: 10.1111/jdv.13179).

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These guidelines encompass different clinical aspects related to actinic keratosis (AK). The primary goal of the guidelines was the development of treatment recommendations appropriate for different subgroups of patients presenting with AK. This was subject to a systematic literature review and a formalized consensus conference including the members of the guidelines' expert panel.

A secondary aim of these guidelines is the implementation of knowledge relating to the clinical background of AK, including recommendations for the histopathological definition, diagnosis and the assessment of patients presenting with AK. Clinical background texts were written by the steering group and subgroups of the expert panel, based on a narrative literature review. Some of these aspects (diagnosis, histopathology, assessment of patients with AK) were formally consented as recommendations during the consensus conference.

The guidelines were elaborated along adapted recommendations by the WHO guidelines review committee[1] and the quality criteria for guidelines as suggested by the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument[2] were incorporated into the methodological development of the guidelines. For the planning and elaboration of the underlying systematic literature review on interventions for AK, the methodology suggested by the Cochrane Handbook for Systematic Reviews of Interventions[3], the GRADE working group[4] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[5] was adapted.

1.1. Remarks on the use of guidelines / Disclaimer

These evidence- and consensus based guidelines contain recommendations that were developed to assist clinicians in the care of patients in specific clinical conditions. The treatment recommendations are based on the best available evidence and their development followed a pre-specified, standardized process. Nevertheless, guidelines do not replace the clinicians' knowledge and skills, since guidelines never encompass therapy specifications for all medical decision-making situations. Guidelines should not be deemed inclusive of all proper methods of care nor exclusive of other methods of care reasonably directed to obtaining the same results. Deviation from the recommendations may be justified or inevitable in specific situations. The ultimate judgment regarding patient care must be

individualized and must be made by the physician and patient in light of all presenting circumstances.

Safety aspects that were considered within these guidelines do not represent a comprehensive assessment of all available safety information for the included interventions. They are limited to those aspects chosen for evaluation and the information available in the included clinical trials. Readers must carefully check the information in these guidelines and determine whether the recommendations (e.g. regarding dose, dosing regimens, contraindications, or drug interactions) are complete, correct, up-to-date and appropriate.

International guidelines are intended to be adapted to national or regional circumstances (regulatory approval and availability of treatments, health care provider and insurance systems). Thus, the national medical societies associated with the International League of Dermatological Societies (ILDS) will be responsible for the adoption and implementation of the guidelines on a national level. Particularly, the mode of application of the different treatment options has to be adapted to national approval of the interventions.

1.2. Objectives of the guidelines

Improvement in the care of patients with actinic keratosis
The provision of recommendations that are based on a systematic review of the external evidence and consented by clinical experts during a structured and formalized process aims at improving the medical care of patients presenting with AK. The choice of an adequate evidence-based treatment strategy – adapted to the individual demands – will be facilitated by the provision of recommendations that take into account frequent clinical scenarios.

Improvement of the knowledge on the treatment necessity and on treatment options
The description of the clinical background, histopathological features and assessment of AK intends to raise awareness of the treatment necessity in a broader range of medical specialties and advance concepts of AK towards a more widely accepted definition.

Reduction of percentage of patients with AKs progressing to invasive squamous cell carcinoma
The use of lesion- and field-directed interventions should be optimized by using the most appropriate treatment regarding the extent and type of AK. Along with a clearance of AK lesions and prevention of their recurrence, the provision of evidence-based treatment algorithms intends to decrease the percentage of patients with progression from AK to invasive squamous cell carcinoma (SCC).

Promotion of adherence
Adherence to the therapeutic regimen is a basic element for the treatment success. Knowledge on the suggested interventions, including expectable effects, adverse effects, duration and possible alternatives is indispensable in the communication with patients. These evidence-based guidelines can help patients to make informed decisions and, consequently, improve the patient compliance to their therapeutic regimen.

1.3. Target population

Health care professionals
The primary goal of these guidelines is to assist health care professionals in the choice of the optimal treatment strategy for their patients with consideration of the severity of the disease and the specific circumstances of the individual patient. Target groups include all health care professionals involved in the assessment and treatment of patients with AK, primarily dermatologists, histopathologists and general practitioners (GP). Due to the international

focus of these guidelines and different organizational structures of health care services in different countries, target groups may vary correspondingly.

Patients
Patients who have AK are mainly adult patients, often of advanced age, and treated in outpatient settings. To take frequent clinical situations into account, different patient subgroups were defined, according to the severity of the disease and the medical history of the patients. The primary focus of these guidelines is the assessment and therapy of patients presenting with single AK lesions, multiple lesions or field cancerization. Patients with concomitant immunosuppression are included as a target group requiring a differential therapeutic approach.

1.4. Pharmacoeconomic considerations

There might be significant variability from country to country, not only in regulatory approval and the availability of interventions, but also in terms of health care providers and insurance systems. Thus, these international guidelines are intended to be adapted to the national or regional conditions. Pharmacoeconomic considerations were therefore not considered as part of the reasoning behind the recommendations concerning interventions. These aspects and possible prioritization of certain interventions should be considered when these guidelines are adapted for implementation at a national level.

2. Methods

Werner

A detailed description of the guidelines development process and methodology is presented in the methods and results report of the guidelines, available at JEADV DOI: 10.1111/jdv.13179.

The guidelines project has kindly been supported by the European Skin Cancer Foundation (ESCF). A declaration of conflicts of interest (COI) was required for the participation in the guidelines development. The COI of each person involved in the guidelines development are presented in the methods and results report of the guidelines.

The guidelines development followed a predefined and structured process.

The steering group, composed by experts in the field of guidelines development, assisted the guidelines development process with organization of the guidelines process, development of methodology and the conduct of a systematic review of the literature on interventions for AK. Members of the expert panel were dermatologists and histopathologists, officially nominated by the International League of Dermatological Societies (ILDS). Participation of general practitioners (GP) was highly desirable, but no official GP nominations were received. Various attempts to include the patient perspective into the guidelines were made and one patient from the Charité University Hospital Berlin (Germany) with large personal experience with different AK treatments was invited to participate in the expert panel.

Key questions to be addressed by the guidelines obtained consensus in an online kick-off conference with the members of the expert panel[6]. Different subgroups of patients presenting with AK, who may require different therapeutic approaches were defined. Expert panel members were asked to choose and rate outcomes with respect to their relevance for clinical decisions concerning the choice of treatment of AK. Rating was performed on a scale from 1 to 9 with 1 representing irrelevant and 9 representing critical outcomes, according to the GRADE methodology[6].

A relevant and recent high quality systematic review, a Cochrane review of interventions for AK,[7] was identified and updated. The update search in selected databases was performed along the search strategies used in the Cochrane review. Defined key question were used to frame the eligibility criteria. The inclusion criteria of each individual trial served to categorize the evidence according to the different subgroups of patients. The available evidence and its quality were summarized according to the system recommended by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) working group[4] for each available outcome in each comparison.

Table 1 summarizes the different quality levels of evidence and the approach used to grade the quality of evidence as suggested by the GRADE working group[8]. Criteria that were applied to up- or downgrade the study quality[9-14] are presented in the methods and results report.

Table 1: Summary of the approach used to grade the quality of evidence for each outcome of interest and the quality levels of evidence as suggested by the GRADE working group[8]

Source of body of evidence and Initial rating of quality of a	Factors that may decrease the rating	Factors that may increase the rating	Final quality of the body of evidence for a certain recommendation and implications

body of evidence					
RCT	High	1. Limitations to study quality 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias	1. Large effect 2. Dose-response 3. All plausible confounding would have reduced the demonstrated effect	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
				Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Observational studies	Low			Low (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Any other evidence	Very low			Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

All recommendations were consented during the consensus conference using a formal consensus methodology (nominal group technique)[15]. To simplify the identification of consented recommendations, all consented recommendations are highlighted throughout this guidelines document (grey boxes). Based on the GRADE approach, 5 strengths of recommendations were differentiated, expressed by the wording and symbols as shown in Table 2. The strength of a recommendation had to be based on the quality of the evidence as shown above (high / moderate / low / very low) and the balance of expected undesirable and desirable outcomes[16, 17]. If expert opinion without external evidence was incorporated into the reasoning for making a certain recommendation, the rationale was provided.

Table 2: Strength of recommendations: wording, symbols and implications[16, 17]

Strength	Wording	Symbols	Implications
Strong recommendation for the use of an intervention	"We recommend …"	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation for the use of an intervention	"We suggest …"	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	"We cannot make a recommendation with respect to …"	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no evidence data available, conflicting outcomes, etc.)
Weak recommendation against the use of an intervention	"We suggest not to …"	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	"We recommend not to …"	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

For each recommendation, the quality of consensus in terms of percentage of agreement was measured and documented.

Before publication, the guidelines draft underwent an extensive internal and external review. The external review took place from 24th of March through 5th of May 2014.

Due to the increasing amount of publications, guidelines need to be continually updated to reflect the recent state of evidence. After July 31, 2018, these guidelines will expire. Should important changes occur in the meantime, such as new available interventions, new important evidence or withdrawal of drug licensing, the information contained in the guidelines will be outdated earlier. In these cases, an update issue of the guidelines will be needed earlier. The ILDS will be responsible to initiate an update.

3. Clinical background of AK

This chapter is based on narrative literature reviews and expert opinion. The stated recommendations or implications were not generated on the basis of a systematic literature review. They were elaborated by the steering group and subgroups of the expert panel. Recommendations presented in grey boxes were subject to a formalized consenting procedure during the consensus conference.

3.1. Introduction to the clinical background of AK

Werner

Actinic keratosis (AK, solar keratosis) is a skin disease that typically develops on areas of chronic sun exposed skin. With a prevalence of up to 60% in certain populations, AK is the most common skin lesion with the potential of progression to invasive skin cancer. AKs manifest as rough, scaly papules, feeling like patches of dry skin. Usually, besides the roughness of the skin and some itching, no specific symptoms occur. The skin may be more sensitive to trauma and bleeding can occur more easily. Treatment necessity arises from the inherent risk of malignant progression and the chronic character of the disease. Additional reasons for treatment may include cosmetic considerations and the relief of symptoms. Several treatment options are available, including lesion-directed interventions aimed at the elimination of clinically manifest lesions and field-directed interventions that aim to reduce apparent and latent areas of affected skin within a field of sun damaged skin.

3.2. Definition and nomenclature of AK

Kerl / Röwert-Huber / Sangueza / Werner

Expressions used synonymously for actinic keratosis (AK) include ‘solar keratosis’, ‘senile keratosis’, ‘keratosis senilis’, ‘senile keratoma’, ‘keratoma senile’, ‘keratinocytic intraepidermal neoplasia’,[18] and ‘in situ squamous cell carcinoma Type AK’.[19] AK occurring on the lips is referred to as ‘actinic cheilitis’.[20]

Different conceptions of the definition have emerged during scientific debates on the histopathological and clinical significance of AK.[18] AK is either described as intraepithelial keratinocytic dysplasia (‘precancerous lesion’) that may possibly ‘transform’ into invasive SCC, or as in situ SCC (intraepidermal proliferation of atypical keratinocytes) that may progress to an invasive stage. More recent characterizations of AK tend to accentuate the latter view of AK as ‘superficial SCC’.[18] This view refers to the fact that AK, at the level of cytology, is indistinguishable from SCC and, at the level of molecular biology, has multiple similarities with SCC.[21] Attempts have been made to adapt the nomenclature, owing to the perspective of AK as carcinoma in situ.[19, 22] A classification of AK, as “keratinocytic intraepidermal neoplasia (KIN) 1-3”[22] or “in situ squamous cell carcinoma Type AK I-III”[19] has been suggested.

These guidelines intend advancing the concept of AK towards a widely accepted definition and thus, the recommendations for the definition, terminology and histopathological classification of AK was formally consented by the expert panel during the consensus conference (see Table 3 and Table 5).

Table 3: Recommendations for the terminology and definition of AK

Recommendations for the terminology and definition of AK†	Evidence	Percentage of agreement
The terms “actinic keratosis (AK)”, “keratinocytic intraepidermal neoplasia (KIN)”, and “in situ squamous cell carcinoma type actinic keratosis” can be used synonymously*. Other expressions should be avoided. *In some regions / countries, the term “solar keratosis” is frequently used.	expert consensus	≥90%
Actinic keratosis may be considered a form of “in situ squamous cell carcinoma” of the skin. When communicating with patients, this term should be used with caution, because the term “carcinoma” is associated with morbidity that does not correspond to the diagnosis of AK in most cases. At the moment, it is not possible to predict the transformation of single AK lesions to invasive squamous cell carcinoma.	expert consensus	≥90%

† The use of this clinical nomenclature in the document reflects the views of the guidelines committee and the ILDS recognizes that there are alternative classification schemes in everyday use.

3.3. Pathophysiology of AK

Connolly / Lim / Torezan / Werner

Chronic exposure to UV radiation plays a central role in the pathogenesis of AK,[23-25] as reflected by the term ‘actinic’ (referring to ‘radiation’), and the synonym ‘solar’ keratosis. UVB radiation can lead to direct DNA damage, causing the formation of cyclobutane pyrimidine dimers and pyrimidine-pyrimidone 6,4-photoproducts.[26, 27] As a result of DNA mutations, the function of tumour suppressor proteins such as p53 can be suppressed, leading to a clonal expansion of keratinocytes into an AK.[28, 29] A dysregulation of the p53 pathway seems to play the most important role in the development of AK lesions, as well as in the further development of SCC.[30] Absorption of UVA radiation by skin chromophores results in the generation of reactive oxygen species, which oxydize guanine residues on the DNA; these oxidative products are mutagenic.[31, 32]
Some evidence suggests that infections with human papilloma viruses act as cofactors in the development of AK,[33] especially in combination with DNA alterations induced by UV radiation.[34, 35] The role of human papilloma viruses in AK and SCC development is ascribed to expression of the viral oncoproteins E6 and E7 by infected keratinocytes.[36]

3.4. Risk factors for the development of AK

Connolly / Lim / Torezan / Werner

Risk factors for the development of AK include advanced age, male gender, cumulative sun exposure and fair skin type.[23, 37, 38] Patients with concomitant immunosuppression have a higher risk for developing AK. This has been especially shown in organ transplant recipients, who are chronically immunosuppressed.[39-42] Genetic syndromes associated with impaired

DNA repair mechanisms, or deficiency in melanin biosynthesis, or an increased vulnerability to UV radiation damage, result in a higher risk for the development of AK. These include xeroderma pigmentosum[26] and albinism.[43] Rothmund-Thompson syndrome, a genetic disorder of chromosomal instability, is known to be associated with AK and squamous cell carcinoma.[44]

3.5. Epidemiology of AK

Correia / Foley / Stockfleth / Werner

There are no published population-based incidence rates of people who develop actinic keratosis[45] and prevalence rates of AK display a wide international range. This may be explained by the international variability of risk factors, especially with respect to the level of exposure to UV radiation and the percentage of fair-skinned inhabitants in different populations. Within countries, populations at risk are defined through the major risk factors of increased age and male gender.

Australia, as a country with close proximity to the equator and a large percentage of fair-skinned inhabitants, shows the highest prevalence of AK, with up to 60% of Australians over the age of 40 having AKs.[38, 46, 47] A population-based prevalence study in Nambour, Queensland (26^0S), reported 44% of men and 37% of women aged 20-69 years had at least one solar keratosis on examination of head, neck, hands and arms[48], the most common sites of occurrence. The prevalence of AK in a UK population aged 60 years or over was shown to be 23% and in the same population, the incidence rate was 149 AK lesions per 1000 person-years.[23] Another UK study found 34% of men and 18% of women aged 70 years and more to have AK.[49] The age-adjusted prevalence of AK in a US population was shown to be 6.5%. In men aged 65 to 74 years (a subpopulation from the same study), the prevalence of AK for participants with high and low sunlight exposure was 55% and 19%, respectively.[50] A study on the prevalence of AK in Italy reports a point prevalence of 1.4%, and an increasing prevalence with age: 3.0% of participants aged 75 years or older had AK lesions.[51] For a Japanese population, a prevalence rate of between 203.3 per 100,000 in an urban area and 841.7 per 100,000 in a rural area was described[52]. In a follow-up study of 424 volunteer adult residents of Maryborough, Victoria (37^0S) who were initially lesion-free, 81 (19%) had a prevalent solar keratosis at 12 months.[47]

3.6. The natural history/ treatment necessity of AK

Werner

A recent systematic review of the available literature on the natural history of AK[53] displays AK as a chronic condition with the potential of regression of AK lesions to 'normal' skin on one side and progression of AK lesions to invasive SCC on the other side. According to this review, reliable data on the progression rates of single AK lesions are scarce and important methodological limitations apply to the available studies, so that the actual risk of progression of single AK lesions to invasive SCC remains unclear (data reported on the risk of progression into invasive SCC ranged from 0 to 0.53% per AK lesion per year). Although the rate of regression of single AK lesions was generally seen to be 20 to 30% with up to 63% in one study, spontaneous regression of complete fields of AK were only seen in 0 to 7.2% of patients. One study assessed the rate of recurrences in AK fields after a complete regression and showed recurrences in 57% of the observed fields. With respect to changes of total AK counts in patients or observed fields over time, the systematic review reports very heterogeneous results, with a range from decreases of 53% to increases of 99% from the number of baseline AK lesions.

These data indicate that the presence of AK without adequate treatment is a dynamic but chronic condition, with a low chance of a sustained spontaneous complete regression. Due to the inherent risk of progression to invasive SCC and the lack of prognostic tools concerning the determination of lesions at risk of progression, an adequate treatment of the AK lesions or the affected field is presumed to be necessary.

4. Assessment of AK

This chapter is based on a narrative literature review and expert opinion. The stated recommendations, implications and definitions were not generated on the grounds of a systematic literature review. They were elaborated by the steering group and subgroups of the expert panel. Recommendations and definitions presented in grey boxes were subject to a formalized consenting procedure during the consensus conference.

4.1. Presentation of AK

Connolly / Martin / Swanson / Werner

Clinically, AKs typically present as scaly or keratotic patches, papules or plaques on an erythematous base. Palpation reveals a sand paper-like texture. The diameter usually does not exceed 1cm,[19] although in some patients lesions can be numerous and confluent. Lesions usually have the same colour as the surrounding skin, but may also present as pink, red or brownish patches, papules or plaques.[30] The surrounding skin may show signs of chronic sun damage, including telangiectasias, dyschromia, elastosis and wrinkles.[54]

AK can be asymptomatic or symptomatic; symptoms such as pruritus, burning, or tenderness and even pain may occur. Little research has been done on the impact of the presence of AK on the quality of life. A negative correlation between the total AK lesion count and the Quality of Life (QoL) as measured by the Skindex-29 and KC (keratinocyte cancer)-specific questions was demonstrated.[55] No prospective change in QoL in association with changing numbers of AKs was found.[56] Depending on their clinical and histological appearance, various types of AK have been described, including pigmented, atrophic, bowenoid, lichenoid or hyperkeratotic AKs.[19, 37]

The anatomic distribution of AK reflects the importance of sun light exposure for their development. Over 80% of AKs occur on the upper limbs, head and neck.[37] Areas often affected are the face, ears, bald scalp, dorsal forearms and hands, and lower legs.

AKs may occur as single lesions, as multiple lesions or in the context of field cancerization. Differential therapeutic strategies for the treatment of these distinguishable subgroups of patients are necessary for adequate patient care.[57, 58]

4.2. Diagnostic criteria

4.2.1. Clinical diagnosis and its accuracy

Connolly / Martin / Swanson / Werner

Diagnosis of AK is usually based on clinical examination of the skin. The clinical presentation as described above (see chapter 4.1) and a history of typical risk factors (see chapter 3.4) defines the diagnostic features. A clinical diagnosis reaches positive predictive values of between 74% and 94%.[59-61] The incorporation of dermoscopy into the diagnostic process may lead to positive and negative likelihood ratios of 19.74 and 0.01, respectively, with a concordance between dermoscopy and histological diagnosis of 0.917.[62] Novel non-invasive imaging techniques such as optical coherence tomography and reflectance confocal microscopy show promising preliminary results.[63] By revealing pleomorphism and architectural disruption in the stratum spinosum, reflectance confocal microscopy may enable the clinician to detect subclinical AK in fields of sun damaged skin.[64]

Different clinical severity scales have been suggested for the clinical assessment of AK: Olsen et al, 1991, suggested the following grading system, depending on the grade of

keratosis: grade I, slightly palpable; grade 2, moderately thick and visible; and grade 3, very thick and hyperkeratotic.[65] A slightly modified scale has been presented by Cockerell.[22]

Yet, there are no guidelines for the clinical differentiation of AK and invasive SCC. Increased tenderness and inflammation have been suggested as clinical markers for the likeliness of malignant progression of AK.[66] Further clinical features were proposed in a review of the literature as criteria to distinguish AKs with increased risk of progression to invasive SCC: induration, bleeding and ulceration, enlargement in the diameter and erythema.[67] However, objectively verifiable clinical criteria remain a matter of continuous debate.

Besides the differentiation of AK and (invasive) SCC, possible differential diagnoses of AK include basal cell carcinoma, Bowen's disease, porokeratosis, nevus, verruca vulgaris, discoid lupus erythematosis, large cell acanthoma, psoriasis, solar lentigo, and seborrheic keratosis.[68] Lentigo maligna may be a differential diagnosis for pigmented AK lesions.[69, 70]

Table 4 shows the recommendations for the assessment of AK lesions that were consented by the expert panel.

Table 4: Recommendations for the assessment of AK lesions

Recommendations for the assessment of AK lesions	Evidence	Percentage of agreement
Clinical diagnosis of AK is recommended for most of the lesions.	expert consensus	≥90%
The clinical classification following Olsen et al. (1991)[65] is recommended to be used to assess the severity degree of single AK lesions: • Grade 1: mild (slight palpability, with actinic keratoses felt better than seen) • Grade 2: moderate (moderately thick actinic keratoses that are easily seen and felt) • Grade 3: severe (very thick and/or obvious actinic keratoses)	expert consensus	≥90%
A biopsy and histological assessment is recommended in the following cases: • clinical diagnosis unclear with respect to the underlying disease • clinical diagnosis unclear with respect to the biologic behaviour of the lesion. Clinical parameters that may be indicators of progression of AK to invasive SCC are the following (based on Quaedvlieg et al. 2006)[67]: o Major criteria: ulceration, induration, bleeding, diameter > 1cm, rapid enlargement, erythema o Minor criteria: pain, palpability, hyperkeratoses, pruritus, pigmentation • unresponsive AK lesions (no regression or early recurrence despite adequate therapy)	expert consensus	≥90%

4.2.2. Histological definition and assessment of AK

Kerl / Röwert-Huber / Sangueza / Werner

Architectural disorder and the presence of atypical keratinocytes in the epidermis are the main histological criteria of the AK diagnosis. In advanced lesions, the presence of atypical keratinocytes may extend from the basal layers throughout the entire epidermis.[30] Atypical keratinocytes are characterized by variable size and shape, and nuclear atypia. Further histological features, described by Röwert-Huber et al.[30] are the following: parakeratosis alternating with hyperkeratosis (displaying the defective maturation of the keratinocytes); loss of polarity; small round buds at the basal layer protruding into the papillary dermis (facultative); normal orthokeratotic cornified layer (as the epidermal keratinocytes of the acrosyringia and acrotrichia are spared); acantholysis with suprabasal clefts (facultative). Histological features of AK in the epidermis are almost always combined with solar elastosis in the dermis, and often accompanied by a dermal infiltrate of lymphocytes and plasma cells.[30]

The main histological determinant of the classification of the severity of AK lesions, as suggested by Röwert-Huber, 2007 and Cockerell, 2000, is the extent of the atypical keratinocytes in the epidermis,[22, 30] as shown in Table 5.

Table 5: Recommendations for the histological classification of AK

Recommendations for the histological classification of AK	Evidence	Percentage of agreement
The following histological classification based on Röwert-Huber et al.[30] is suggested to assess the severity degree of single AK lesions: • early in situ SCC, Type AK I corresponds to atypical keratinocytes in the basal and suprabasal layers (the lower third) of the epidermis • early in situ SCC, Type AK II is constituted by atypical keratinocytes extending to the lower two thirds of the epidermis • in situ SCC, Type AK III consists of atypical keratinocytes extending to more than two thirds of the full thickness of the epidermis	expert consensus	≥75%

4.2.3. Other diagnostic means

Kerl / Sangueza / Röwert-Huber / Werner

Immunohistochemical tests do not play an important role in the assessment of AK. The helpfulness of melanocytic markers for the differentiation of pigmented AK lesions from melanocytic proliferations remains a matter of debate.[71-73]

4.3. Subgroups of patients presenting with AK

Werner

A widely agreed upon definition of degrees of the overall severity of AK could not be identified. Different subgroups of patients presenting with AK, requiring differential therapeutic approaches were defined at the beginning of the guidelines development in order to address the demands of clinical practice. The definitions were discussed and consented during the kick-off consensus conference (Table 6).

Table 6: Recommendations for a classification of patients according to the severity of AK

Recommendations for a classification of patient subgroups:	Evidence	Percentage of agreement
The following subgroups of patients should be considered separately: • Patients with single AK lesions • Patients with multiple AK lesions • Patients with field cancerization • Patients with concomitant immunosuppression	expert consensus	≥90%
Definition of patients presenting with single AK lesions: At least one and not more than five palpable or visible AK lesions per field or affected body region	expert consensus	≥90%
Definition of patients presenting with multiple AK lesions: At least 6 distinguishable AK lesions in one body region or field	expert consensus	≥90%
Definition of patients presenting with field cancerization: At least 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis	expert consensus	≥90%
Definition of immunosuppressed patients with AK: AK at any of the above-mentioned severity degrees and concomitant immunosuppression (e. g. due to chronic immunosuppressive medication or specific diseases affecting the function of the immune system, such as malignant hematologic disorders)	expert consensus	≥90%

5. Available treatment options

The following treatment options were selected as relevant interventions for actinic keratosis by the authors of these guidelines in consensus with ≥ 75% of the expert panel members to be included in the assessment and evaluation. The selection of interventions and their mode of application served as inclusion criteria for the systematic literature assessment. Other interventions and other application modes for the selected interventions were not included into the systematic literature review. This does not imply that other interventions are not possibly suitable for the treatment of AK. Modes of application of the listed interventions might have to be adapted when implementing the guidelines in the national context. When deciding for using certain interventions, users of this guidelines must carefully check the treatment option and its mode of application, e.g. regarding approval status, dose, dosing regimen, adverse effects, contraindications, or drug interactions.

5.1. Treatment options selected for evaluation

Lesion-directed treatment options for AK aim at the physical destruction or removal of atypical keratinocytes that constitute a singular AK lesion. These treatments are directed towards the clinically manifest (visible or palpable) AK lesions. Field-directed treatment options for AK similarly aim at the destruction, removal or remission of atypical keratinocytes. Here, therapy of latent, subclinical areas of atypical keratinocytes within a field of chronic sun damaged skin and not only a reduction of manifest areas of AK is intended. Classification of the interventions along these categories is difficult in some cases. For the recommendations, all listed interventions were considered for all types of patients.

Table 7 shows a list of treatment options for AK that were selected for evaluation within this clinical guideline. Please note that the stated mode of application does not imply guidance for the mode of use of the listed interventions, but solely reflects the criteria that had to be fulfilled for inclusion into the systematic review.

Table 7: Treatment options selected for evaluation

Intervention	**Mode of application**
Curettage	Once, repeated up to 2 times
Cryotherapy	Once, repeated up to several times
Carbon dioxide (CO2) laser	Once, repeated up to several times
Er:YAG laser	Once, repeated up to several times
0.5% 5-fluorouracil + 10% salicylic acid	Once daily application for 6 to 12 weeks
5-aminolaevulinic acid photodynamic therapy (ALA-PDT)*	Different concentrations, light sources and application modes of ALA-PDT were included, incubation time had to be at least 1 hour
Methylaminolevulinate photodynamic therapy (MAL-PDT)*	Different light sources and application modes of MAL-PDT were included, incubation time had to be at least 2.5 hours
3% diclofenac in 2.5% hyaluronic acid gel	Twice daily application for 60 to 90 days
0.5% 5-fluorouracil (0.5% 5 FU)	Once daily for 1 to 4 weeks
5% 5-fluorouracil (5% 5 FU)	Once or twice daily for 2 to 4 weeks
2.5% Imiquimod	Once daily application for 2 weeks followed by a

	rest period of two weeks (One or two treatment cycles)
3.75% Imiquimod	Once daily application for 2 weeks followed by a rest period of two weeks (One or two treatment cycles)
5% Imiquimod	Once daily application at 2 or 3 days per week for a time period of 4-16 weeks; continuously or intermittent.
0.015% Ingenol mebutate for lesions on the face or scalp	Once daily application for 3 days
0.05% Ingenol mebutate for lesions on the trunk or extremities	Once daily application for 2 days

* PDT often included pretreatment of the AK lesions, e.g. with curettage or other topical interventions. These were not classified as 'combination treatments' (see chapter 5.2), unless the combination included one of the other selected interventions (except for curettage). For information on the specific mode of application of PDT in the included studies, see results report (online supplement).

5.2. Combined treatment options

The expert panel suggested different (sequential) combinations of interventions for the treatment of AK. Although these were initially intended to be assessed within the systematic literature review, the expert panel and steering group decided not to include combined treatment options into the systematic literature assessment. A subgroup from the expert panel summarized the available evidence (not exclusively based on the systematic literature assessment) regarding reasonable combinations that may increase the efficacy through synergistic effects (please see chapter 9).

6. Assessment of treatment options/ rating of outcomes

To be included into the systematic review, studies had to report at least one of the selected outcomes. Outcomes had to be reported as events per patients in case of dichotomous outcomes (the number of events and the number of patients at the time of assessment had to be reported) or as mean difference in case of continuous outcomes (the mean and standard deviation had to be reported). Otherwise studies could not be considered. Efficacy assessment was accomplished for all comparisons. Safety outcomes, patient reported outcomes, and cosmetic outcomes were only assessed for head-to-head comparisons (RCTs with active control).

6.1. Efficacy

The following efficacy outcomes were assessed:

- Mean reduction in lesion counts from baseline to assessment (absolute values [preferred] or percentages)
- Participant complete clearance (CC, rate of participants with a complete clearance of all lesions within a predefined field)
- Participant partial clearance (PC, rate of participants with at least a 75% reduction of the AK lesion counts within a predefined field)
- Investigator global improvement index (IGII, rate of participants rated as 'completely improved' by the investigator)
- Participants global improvement index (PGII, rate of participants self-assessed as 'completely improved').

For reasons of feasibility and to allow for comparability, the efficacy outcomes had to be reported 2 months after the end of treatment or whatever was closest, not more than 6 months after the end of treatment. Studies examining longer treatment periods were not included in the systematic review. All efficacy outcomes were rated as critical outcomes.

6.2. Tolerability/ safety

The following safety outcomes were assessed for every head-to-head-comparison:

- Withdrawals due to adverse events
- Skin irritation

Due to the numerous different safety outcomes that were assessed for the different comparisons of interventions, experts could chose up to three further safety outcomes for each comparison. For the comparison of cryotherapy with 5% imiquimod, the following outcomes were chosen (example):

- Erosion/ulceration
- Infection
- Blister formation

The rate of events for all safety outcomes refers to events that occurred from baseline until the end of the study. Withdrawals due to adverse events and skin irritation were rated as critical outcomes for all comparisons of interventions. All other safety outcomes that were selected for specific comparisons were rated as important outcomes.

6.3. Patient reported outcomes

The following patient reported outcomes were assessed for head-to-head-comparisons:

- Participant's satisfaction (rate of participants 'satisfied' or 'very satisfied)
- Participant's preference (rate of participants preference)
- Compliance

If more than one assessment of patient reported outcomes was performed in a study, the final assessment was chosen for evaluation. Participant's preference could only be assessed in split-patient trials. All patient-reported outcomes were rated as 'critical outcomes'.

6.4. Cosmetic outcomes

For all head-to-head comparisons, members of the expert panel could choose three cosmetic outcomes. The following selection of cosmetic outcomes was made for the comparison of ALA-PDT with 0.5% 5-fluorouracil (example):

- Improvement in global response
- Improvement in tactile roughness
- Improvement in mottled hyperpigmentation

If more than one assessment of cosmetic outcomes was performed in a study, the final assessment was chosen for evaluation. Apart from 'excellent global cosmetic outcome' for the comparisons of cryotherapy with 5% 5-fluorouracil and cryotherapy with 5% imiquimod, all cosmetic outcomes that were selected for evaluation were rated as 'important outcome'.

6.5. Other considerations

Other considerations could be included into the reasoning for making recommendations for specific interventions. These could include expert experience concerning resource use, practicability, adherence or other reasons. These considerations were not assessed systematically. They were discussed during the consensus conference and stated for each recommendation as 'additional reasoning'.

7. Overview: Recommendations for the treatment of AK

		single AK lesions ≥ 1 and ≤ 5 palpable or visible AK lesions per field or affected body region	**multiple AK lesions** ≥ 6 distinguishable AK lesions in one body region or field	**field cancerization** ≥ 6 AK lesions in one body region or field, and contiguous areas of chronic actinic sun damage and hyperkeratosis	**Immunocompromised patients with AK** AK at any of the mentioned severity degrees and a concomitant condition of immunosuppression
		Sun protection in all patient subgroups!			
Strength of recommendation	↑↑	Cryotherapy	0.5% 5-FU 3.75% imiquimod Ingenol mebutate 0.015% / 0.05% MAL-PDT, ALA-PDT		-
	↑	Curettage* 0.5% 5-FU, 5% 5-FU 0.5% 5-FU + 10% SA* 3.75% imiquimod 5% imiquimod ingenol mebutate 0.015/0.05% ALA-PDT, MAL-PDT	Cryotherapy** 3% diclofenac in 2.5% HA 5% 5-FU 0.5% 5-FU + 10% SA* 5% imiquimod, 2.5% imiquimod CO2-laser, Er:YAG-laser		cryotherapy** curettage* 5% 5-FU 5% imiquimod*** ALA-PDT, MAL-PDT
	0	3% diclofenac in 2.5% HA 2.5% imiquimod CO2-laser, Er:YAG-laser	Curettage*		3% diclofenac in 2.5 % HA 0.5% 5-FU 0.5% 5-FU + 10% SA 2.5% imiquimod, 3.75% imiquimod Ingenol mebutate 0.015%/0.05%
	↓	-	-		CO2-laser, Er:YAG-laser

* discrete, hyperkeratotic AK lesions
** single or multiple discrete AK lesions, not for treatment of field cancerization
*** For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.

8. Results and recommendations

For a more comprehensive and detailed description of the results from the systematic literature search and assessment, please consider the methods and results report of the guidelines (available at JEADV DOI: 10.1111/jdv.13179). The information reported in the included studies did not allow to distinguish between the subgroups of patients with multiple AK lesions and patients with field cancerization. Therefore, these two subgroups were generally pooled together in order to make treatment recommendations.

8.1. Curettage

No data were eligible for this intervention.

Curettage is particularly useful for treating hypertrophic AK of the extremities. It can be used in conjunction with shave excision, electrodessication (ED&C) or cryotherapy. If the possibility of an invasive SCC is suspected, a shave excision or biopsy of a suspicious lesion should be performed in conjunction with curettage. The disadvantage of curettage is that only a limited number of visible lesions can be treated, local anesthesia is required, healing times are prolonged especially on the lower extremities, prolonged hyperpigmentation can occur and depigmentation and scarring are expected.

Performing curettage for discrete hyperkeratotic lesions is a very common practice and especially in hyperkeratotic lesions, other interventions are less likely to work due to insufficient penetration into the skin. Despite the long experience with performing curettage, due to the missing external evidence a weak recommendation was made for the curettage of discrete, hyperkeratotic AK lesions in patients with single lesions and in immunosuppressed patients with AK.

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using curettage for discrete, hyperkeratotic lesions in patients with single AK lesions.	↑	≥90%
We cannot make a recommendation with respect to curettage in patients with multiple AK lesions or field cancerization.	0	≥90%
We suggest using curettage for discrete, hyperkeratotic lesions in immunosuppressed patients.	↑	≥75%

8.2. Cryotherapy

- No placebo-controlled trials were eligible for cryotherapy.
- Compared to 5% 5-fluorouracil in a sample of participants with multiple AK lesions / field cancerization[74], cryotherapy was inferior concerning participants' complete clearance (RR: 0.71; 95%-CI: 0.54 – 0.94; GRADE: low quality) and 'better skin appearance' (RR: 0.27; 95%-CI: 0.11 – 0.72; GRADE: moderate quality). No statistically significant differences were seen with respect to 'excellent global cosmetic outcome' (RR: 0.96; 95%-CI: 0.06 -14.5; GRADE: low quality).
- Compared to 5% imiquimod in samples of participants with multiple AK lesions / field cancerization[74, 75], cryotherapy was inferior concerning the rate of an 'excellent cosmetic outcome' (RR: 0.05; 95%-CI: 0.01 – 0.34; GRADE: moderate quality) and

'better skin appearance' (RR: 0.19; 95%-CI: 0.08 – 0.47; GRADE: moderate quality). A statistically significant higher rate of blister formation was seen in the cryotherapy group (RR: 20.43; 95%-CI: 1.24 – 335.9; GRADE: low quality). No statistically significant differences were seen with respect to complete clearance (RR: 0.80; 95%-CI: 0.59 – 1.10; GRADE: low quality), withdrawals due to adverse events (RR: 0.49; 95%-CI: 0.10 – 2.49; GRADE: moderate quality), erosion / ulceration (RR: 1.75; 95%-CI: 0.65 – 4.71; GRADE: low quality), and rates of infection (RR: 0.49; 95%-CI: 0.05 – 5.12; GRADE: low quality).

- Compared to MAL-PDT in samples including participants with single and multiple AK lesions / field cancerization[76-79], cryotherapy was inferior concerning an "excellent or good cosmetic outcome" as rated by the investigator (RR: 0.84; 95%-CI: 0.74 – 0.95; GRADE: very low quality), patient preference (RR: 0.42; 95%-CI: 0.29 – 0.63; GRADE: low quality) and satisfaction (RR: 0.41; 95%-CI: 0.27 – 0.61; GRADE: very low quality). No statistically significant differences were seen with respect to withdrawals due to AE (RR: 1.06; 95%-CI: 0.16 – 7.16; GRADE: very low quality) and participant's rating of the cosmetic outcome as 'excellent or good' (RR: 0.93; 95%-CI: 0.86 – 1.01; GRADE: low quality). For photosensitivity reaction, a lower rate was seen in the cryotherapy group (RR: 0.01; 95%-CI: 0 – 0.15; GRADE: very low quality). For the event 'cold exposure injury', a higher rate was seen in the cryotherapy group (RR: 151; 95%-CI: 9.47 – 2409; GRADE: very low quality).
- Compared to ALA-PDT in a sample including participants with single and multiple AK lesions / field cancerization[80], cryotherapy had a lower rate of skin irritation (RR: 0.27; 95%-CI: 0.16 - 0.46; GRADE: low quality), but cryotherapy was inferior concerning the rate of complete clearance (RR: 0.76; 95%-CI: 0.61 to 0.96; GRADE: very low quality).

Cryotherapy is a widely used and long established treatment option and experts confirm a very good clinical efficacy for single lesions. The low costs (resource use), availability and good compliance (due to the treatment mode) are further arguments for the use of cryotherapy. Based on these considerations the expert group felt that a strong recommendation for patients with single AK lesions is well justified. For the use of cryotherapy for discrete lesions in immunosuppressed patients, analogue considerations led to the weak recommendation.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We recommend using cryotherapy in patients with single AK lesions.	↑↑	≥75%
We suggest using cryotherapy in patients with multiple lesions, especially for multiple discrete lesions. Cryotherapy is not suitable for the treatment of field cancerization.	↑	≥90%
We suggest using cryotherapy in immunosuppressed patients, especially for single lesions or multiple discrete lesions. Cryotherapy is not suitable for the treatment of field cancerization.	↑	≥75%

8.3. Carbon dioxide (CO_2) laser and Er:YAG laser

- No placebo controlled trials were eligible for CO_2 or Er:YAG laser
- Compared to 5% 5-fluorouracil in a sample of participants with multiple AK lesions / field cancerization[81], CO_2 laser did not show statistically significant differences concerning the reduction in lesion counts (GRADE: very low quality) and withdrawals due to adverse events (GRADE: very low quality). For details see chapter 8.6.

- Compared to ALA-PDT in a sample of participants with multiple AK lesions / field cancerization[82], CO_2 laser was not statistically significantly different concerning participants' preference (GRADE: very low quality). For details see chapter 8.11.

Experts evaluate CO_2 laser as an effective treatment with respect to long-term efficacy. Efficacy and safety of CO_2 laser depend on the user's experience due to a lack of standardization of its application. Most common risks of using CO_2 laser are infections, scarring, and hyper-/hypopigmentation of the treated areas. Immunosuppressed patients are more susceptible to skin infections, and thus experts suggest not using CO_2 laser for the treatment of AK in immunosuppressed patients; in spot areas CO_2 laser might still be used.
For Er:YAG laser, experts decided to adapt the recommendations made for CO_2 laser. Two aspects should be considered: Er:YAG laser does not penetrate the epidermis as well as CO_2 laser does, hence it is not suitable for the treatment of hyperkeratotic lesions; furthermore Er:YAG laser does not provide coagulation and therefore the risk of bleeding is higher.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We cannot make a recommendation with respect to CO_2 laser and Er:YAG laser in patients with single AK lesions.	0	≥75%
We suggest using CO_2 laser or Er:YAG laser in patients with multiple AK lesions or field cancerization.	↑	≥50%*
We suggest not to use CO_2 laser or Er:YAG laser in immunosuppressed patients.	↓	≥75%
**Experts who did not agree to this recommendation voted for making no recommendation (0) for the use of this intervention in patients with multiple lesions or field cancerization.*		

8.4. 3% diclofenac in 2.5% hyaluronic acid gel

- Compared to 2.5% hyaluronic acid gel (vehicle) in samples of immunocompetent patients with multiple lesions / field cancerization[83-86], 3% diclofenac in 2.5% hyaluronic acid gel was superior concerning participants' complete clearance (RR: 2.35; 95%-CI: 1.65 - 3.34; GRADE: moderate quality), mean reduction in AK lesion counts (mean difference: 3.00; 95%-CI: 1.64 - 4.36; GRADE: low quality), Participant global improvement index (PGII) rated as 'completely improved' (RR: 2.57; 95%-CI: 1.51 - 4.36; GRADE: moderate quality), and Investigator global improvement index (IGII) rated as 'completely improved' (RR: 2.65; 95%-CI: 1.60 - 4.39; GRADE: moderate quality).
- Compared to 2.5% hyaluronic acid gel (vehicle) in a sample of immunosuppressed patients[87], no statistically significant differences were seen with respect to the rate of complete clearance (RR: 5.78; 95%-CI: 0.38 - 87.35; GRADE: very low quality) and the rate of partial clearance (RR: 3.55; 95%-CI: 0.57 - 21.94; GRADE: low quality).
- Compared to 5% imiquimod in a sample of patients with single AK lesions[88], no statistically significant differences were seen concerning participants' complete clearance (RR: 0.95; 95%-CI: 0.27 - 3.30; GRADE: low quality).
- Compared to 5% imiquimod in a sample of patients with single and multiple AK lesions / field cancerization[89], no statistically significant differences were seen concerning Investigator global improvement index (IGII) rated as 'completely improved' (RR: 0.52; 95%-CI: 0.15 - 1.85; GRADE: very low quality), Participant global improvement index (PGII) rated as 'completely improved' (RR: 1.22; 95%-CI: 0.48 - 3.10; GRADE: very low quality), erythema (RR: 1.15; 95%-CI: 0.60 - 2.19; GRADE: very low quality), crusting (RR: 1.82; 95%-CI: 0.61 - 5.44; GRADE: very low quality), and scaling (RR: 0.69; 95%-CI: 0.13 - 3.80; GRADE: very low quality).

- Compared to 0.5% 5-fluorouracil in 10% salicylic acid in a sample of patients with single and multiple lesions / field cancerization[90], 3% diclofenac was inferior concerning participants' complete clearance (GRADE: low quality), participant's global assessment as "good/very good" (GRADE: very low quality) and physician's global assessment of the clinical improvement as "good/very good" (GRADE: very low quality). Less minor adverse events occurred in the diclofenac group with respect to application-site irritation (GRADE: low quality), treatment emergent adverse events (GRADE: very low quality) and administration site reaction (GRADE: low quality). No statistically significant difference was seen with respect to the rate of infections and infestations (GRADE: very low quality). For details see chapter 8.13.

Experts perceive the long-term efficacy of 3% diclofenac in 2.5% hyaluronic acid as much poorer than long-term efficacy of other topical treatments. Diclofenac might be more effective in certain areas (e.g. face) than in others. Experts also perceive that the treatment duration of 60 to 90 days with twice daily use imposes a negative impact on the practicability and might affect the adherence, although there is some contradictory evidence to that from a randomized trial.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We cannot make a recommendation with respect to 3% diclofenac in 2.5% hyaluronic acid gel for patients with single AK lesions.	0	≥75%
We suggest using 3% diclofenac in 2.5% hyaluronic acid gel in patients with multiple AK lesions or field cancerization.	↑	≥75%
We cannot make a recommendation with respect to 3% diclofenac in 2.5% hyaluronic acid gel for immunosuppressed patients.	0	≥90%

8.5. 0.5% 5-fluorouracil (0.5% 5-FU)

- Compared to its vehicle in samples of patients with multiple lesions / field cancerization[91-93], 0.5% fluorouracil was superior concerning participants' complete clearance (RR: 8.86; 95%-CI: 3.67 - 21.40; GRADE: low quality) and mean reduction in lesion counts (mean difference: 5.40; 95%-CI: 2.94 - 7.86; GRADE: high quality.)
- The 0.5% fluorouracil cream concentration was preferred to the 5% concentration (RR: 5.67; 95%-CI: 1.96 - 16.35; GRADE: moderate quality) in one trial[94]. No statistically significant differences were found with respect to the minor adverse events erythema (RR: 1.00; 95%-CI: 0.91 - 1.09; GRADE: moderate quality), erosion (RR: 0.85; 95%-CI: 0.68 - 1.07; GRADE: low quality), and pain (RR: 0.75; 95%-CI: 0.40 - 1.39; GRADE: low quality).
- Compared to ALA-PDT in a sample of patients with single and multiple AK lesions / field cancerization[95], no statistically significant differences were seen with respect to the rate of complete clearance (GRADE: very low quality), partial clearance (GRADE: very low quality), withdrawals due to adverse events (GRADE: very low quality), improvement in global response (GRADE: very low quality), improvement in tactile roughness (GRADE: very low quality), and improvement in mottled hyperpigmentation (GRADE: very low quality). For details see chapter 8.11.

For patients with single AK lesions, indirect evidence from the good data on the efficacy of 0.5% 5-FU in multiple lesions patients was drawn to make a weak recommendation; additionally with regards to the evidence for the multiple lesions treatment, experts highlighted data from a network analysis showing the good efficacy of 5-FU compared to the other interventions for complete clearance.[96]

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using 0.5% fluorouracil in patients with single AK lesions.	↑	≥75%
We recommend using 0.5% fluorouracil in patients with multiple AK lesions or field cancerization.	↑↑	≥50%*
We cannot make a recommendation with respect to 0.5% fluorouracil for immunosuppressed patients.	0	≥75%
** Experts who did not agree voted for making a weak recommendation (↑) for the use of 0.5% 5-fluorouracil in patients with multiple lesions or field cancerization.*		

8.6. 5% 5-fluorouracil (5% 5-FU)

- No data were eligible for the comparison of 5% 5-fluorouracil with vehicle.
- Compared to the 0.5% fluorouracil cream concentration, participants preferred the 0.5% fluorouracil concentration to the 5% concentration[94] (GRADE: moderate quality). No statistically significant differences were seen with respect to the minor adverse events erythema (GRADE: moderate quality), erosion (GRADE: low quality), and pain (GRADE: low quality). For details see chapter 8.5.
- Compared with cryotherapy in a sample of participants with multiple AK lesions / field cancerization[74], 5% 5-FU was statistically significantly superiority with respect to complete clearance (small effect size, uncertain clinical importance; GRADE: low quality) and the cosmetic outcome of "better skin appearance" (GRADE: moderate quality). No difference was seen with respect to the "excellent cosmetic outcome" (GRADE: low quality). For details see chapter 8.2.
- Compared to 5% imiquimod in samples of participants with single and multiple AK lesions / field cancerization[74, 97], no statistically significant differences concerning complete clearance were seen (GRADE: very low quality). 5% imiquimod was significantly more frequently associated with an 'excellent' cosmetic outcome as rated by the investigator (GRADE: low quality) and with a normal skin surface (GRADE: low quality; statistically significant result of uncertain clinical importance). With respect to the withdrawals due to adverse events, no effect estimate could be calculated (no events in both study groups). For details see chapter 8.9.
- Compared to CO_2-laser in a sample of participants with multiple AK lesions / field cancerization[81], no statistically significant differences were seen with respect to the mean percent reduction of the AK lesion counts (mean difference -8.8%; 95%-CI: -20.7% - 3.16%; GRADE: very low quality) and to the number of withdrawals due to AE (RR: 0.18; 95%-CI: 0.01 - 3.27; GRADE: very low quality).

The weak recommendation for using 5% 5-fluorouracil cream in patients with single and multiple AK lesions and patients with field cancerization is based on clinical long-term experience through wide-spread use in many countries and the non-inferiority of topical 5% 5-FU with respect to head-to-head comparison with imiquimod 5%, cryotherapy and CO_2 laser.
With respect to immunosuppressed patients, the weak recommendation is similarly based on clinical long-term experience through the wide-spread use in many countries. Additionally, there is a good expert agreement that the cytotoxic mechanism of action without direct modulation of the immune system is safer for the use in immunosuppressed patients than e.g. imiquimod.

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using 5% fluorouracil in patients with single AK lesions.	↑	≥50%*
We suggest using 5% fluorouracil in patients with multiple AK lesions or field cancerization.	↑	≥50%**
We suggest using 5% fluorouracil in immunosuppressed patients.	↑	≥75%
** Experts who did not agree voted for making a strong recommendation (↑↑) or no recommendation (0) for the use of 5% 5-fluorouracil in patients with single AK lesions.*		
*** Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% 5-fluorouracil in patients with multiple lesions or field cancerization.*		

8.7. 2.5% Imiquimod

- Compared to its vehicle in a sample of participants with multiple AK lesions / field cancerization[98], 2.5% imiquimod cream was statistically significantly superior with respect to the rate of complete clearance (RR: 4.87; 95%-CI: 2.59 - 9.27; GRADE: high quality) and the rate of partial clearance (RR: 2.13; 95%-CI: 1.53 - 2.95; GRADE: high quality).
- Compared to the 3.75% imiquimod cream concentration, no statistically significant difference was seen concerning the rate of complete clearances[98] (RR: 0.86; 95%-CI: 0.63 - 1.18; GRADE: moderate quality). With respect to the rate of partial clearance, the confidence interval touches the line of no effect (RR: 0.81; 95%-CI: 0.66 to 1.00; GRADE: moderate quality). No statistically significant differences were seen concerning the withdrawals due to adverse events (RR: 0.50; 95%-CI: 0.05 - 5.46; GRADE: moderate quality), application site irritation (RR: 0.80; 95%-CI: 0.22 - 2.92; GRADE: moderate quality), application site pruritus (RR: 0.86; 95%-CI: 0.29 - 2.49; GRADE: moderate quality), application site pain (RR: 0.40; 95%-CI: 0.08 - 2.03; GRADE: moderate quality), and application site swelling (RR: 0.20; 95%-CI: 0.01 - 4.13; GRADE: moderate quality).

Because of limited experience with this concentration of imiquimod and the lower efficacy concerning partial clearance rates when compared to the 3.75% concentration of imiquimod, a weak recommendation was made for patients with multiple AK lesions or field cancerization.

Recommendation	Strength of recommendation	Percentage of agreement
We cannot make a recommendation with respect to 2.5% imiquimod for patients with single AK lesions.	0	≥90%
We suggest using 2.5% imiquimod in patients with multiple AK lesions or field cancerization.	↑	≥75%
We cannot make a recommendation with respect to 2.5% imiquimod for immunosuppressed patients.	0	≥90%

8.8. 3.75% Imiquimod

- Compared to its vehicle in a sample of participants with multiple AK lesions / field cancerization[98], 3.75% imiquimod cream was statistically significantly superior with respect to the rate of complete clearance (RR: 5.66; 95%-CI: 3.00 - 10.69; GRADE: high quality) and the rate of partial clearance (RR: 2.62; 95%-CI: 1.91 - 3.59; GRADE: high quality).
- Compared to the 2.5% imiquimod cream concentration, no statistically significant difference was seen concerning the rate of complete clearances[98] (GRADE: moderate quality). With respect to the rate of partial clearance, the confidence interval touches the line of no effect (GRADE: moderate quality). No statistically significant differences were seen concerning the withdrawals due to adverse events (GRADE: moderate quality), application site irritation (GRADE: moderate quality), application site pruritus (GRADE: moderate quality), application site pain (GRADE: moderate quality), and application site swelling (GRADE: moderate quality). For details see chapter 8.7.

Due to the long-term experience with the 3.75% imiquimod cream concentration and drawing indirect evidence from the efficacy of 3.75% imiquimod in patients with multiple AK lesions, a weak recommendation was made for patients with single AK lesions although no trials including this population were eligible.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 3.75% imiquimod in patients with single AK lesions.	↑	≥90%
We recommend using 3.75% imiquimod in patients with multiple AK lesions or field cancerization.	↑↑	≥90%
We cannot make a recommendation with respect to 3.75% imiquimod for immunosuppressed patients.	0	≥90%

8.9. 5% Imiquimod

- Compared to its vehicle in samples of immunocompetent participants with single AK lesions and multiple AK lesions / field cancerization[99-108], 5% imiquimod cream was statistically significantly superior with respect to the rate of complete clearance (RR: 8.55; 95%-CI: 4.80 - 15.23; GRADE: low quality) and the rate of partial clearance (RR: 6.53; 95%-CI: 3.54 - 12.03; GRADE: low quality). In one study with a small sample size[106], no statistically significant difference concerning the mean reduction of AK lesion count was seen (mean difference 2.2 lesions; 95%-CI: -1.05 to +5.45; GRADE: low quality).
- Compared to its vehicle in a sample of immunosuppressed organ transplant recipients[109], participants randomized to the imiquimod 5% treatment group had a statistically significantly higher rate of complete clearance (RR: 18.50; 95%-CI: 1.19 - 286.45; GRADE: low quality) and of partial clearance (RR: 23.50; 95%-CI: 1.53 - 360.94; GRADE: low quality).
- Compared to cryotherapy, no statistically significant differences were seen with respect to the rate of complete clearance[74, 75] (GRADE: low quality), withdrawals due to adverse events (GRADE: moderate quality), erosion / ulceration, and infection (GRADE: low quality). 5% imiquimod was superior to cryotherapy with respect to the rate of blister formation (GRADE: low quality), “excellent cosmetic outcome” (GRADE:

moderate quality) and “better skin appearance” (GRADE: moderate quality). For details see chapter 8.2.

- Compared to 3% diclofenac gel in a sample of participants with single AK lesions[88], no statistically significant differences were found with respect to the rate of complete clearance (GRADE: low quality). Effect size and confidence interval concerning the rate of withdrawals due to adverse events could not be calculated due to no events in both groups. For details see chapter 8.4.
- Compared to 3% diclofenac gel in a sample of participants with single or multiple AK lesions / field cancerization[89], no statistically significant differences were found with respect to the rate of participants with the Investigator global improvement index (IGII) rated as ‘completely improved’ (GRADE: very low quality) and with respect to the rate of participants with the Participant global improvement index (PGII) rated as ‘completely improved’ (GRADE: very low quality). Concerning minor adverse events that were assessed during the study period, no statistically significant differences were seen, with respect to: Erythema (GRADE: very low quality), crusting (GRADE: very low quality), and scaling (GRADE: very low quality). For details see chapter 8.4.
- Compared to 5% fluorouracil in samples of participants with single and multiple AK lesions / field cancerization[74, 97], no statistically significant differences concerning complete clearance were seen (RR: 0.54; 95%-CI: 0.12 - 2.43; GRADE: very low quality). 5% imiquimod was significantly more frequently associated with an ‘excellent’ cosmetic outcome as rated by the investigator (RR: 19.38; 95%-CI: 2.82 - 133.26; GRADE: low quality) and with a normal skin surface (RR: 1.45; 95%-CI: 1.00 - 2.11; GRADE: low quality; statistically significant result of uncertain clinical importance). With respect to the withdrawals due to adverse events, no effect estimate could be calculated (no events in both study groups).
- Compared to ALA-PDT in a sample of participants with multiple AK lesions / field cancerization[110], participants preferred ALA-PDT over 5% imiquimod cream on a statistically significant level (GRADE: moderate quality). No statistically significant differences were seen with respect to the minor adverse event “erythema” (GRADE: moderate quality). Statistically significantly less minor adverse events occurred in the imiquimod treated areas, with respect to “burning” (GRADE: moderate quality), “pain” (GRADE: low quality), and “oedema” (GRADE: moderate quality). For details see chapter 8.11.
- Compared to MAL-PDT in samples of participants with multiple AK lesions / field cancerization[111, 112], no statistically significant difference was seen concerning efficacy: complete clearance (GRADE: low quality) and partial clearance rates (GRADE: low quality). A statistically significantly lower rate of participants was ‘very satisfied’ with 5% imiquimod than with MAL-PDT (GRADE: moderate quality). For details see chapter 8.12.

For patients with multiple AK lesions / field cancerization, a weak recommendation was made (as compared to the strong recommendation for the 3.75% concentration of imiquimod cream). Besides the lower quality of evidence for 5% imiquimod, experts perceive the tolerability of 3.75% imiquimod as better due to the shorter duration and lower intensity of side effects.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 5% imiquimod in patients with single AK lesions.	↑	≥75%
We suggest using 5% imiquimod in patients with multiple AK lesions or field cancerization.	↑	≥75%

We suggest using 5% imiquimod in immunosuppressed patients with AK.*	↑	≥50%**
** For immunosuppression, different clinical situations may exist, e.g. iatrogenic medical immunosuppression after organ transplantation, iatrogenic medical immunosuppression because of autoimmune disorders, immunosuppression due to other reasons (hematologic disorders, AIDS etc). Depending on the underlying disease, special care has to be given to the selection of the treatment to avoid (auto-) immunstimulation that may lead to a worsening of the underlying condition.* *** Experts who did not agree voted for making a strong recommendation (↑↑) for the use of 5% imiquimod in immunosuppressed patients.*		

8.10. Ingenol mebutate

- Compared to its vehicle in a sample of participants with single AK lesions and multiple AK lesions / field cancerization[113], ingenol mebutate 0.015% for the treatment of lesions on the face or scalp was statistically significantly superior with respect to complete clearance (RR: 11.40; 95%-CI: 6.11 - 21.28; GRADE: moderate quality), partial clearance (RR: 8.63; 95%-CI: 5.61 - 13.27; GRADE: moderate quality) and percent reduction in AK lesion counts (mean difference: 58.06%; 95%-CI: 52.52 – 63.60% higher; GRADE: moderate quality).
- Compared to its vehicle in samples of participants with single AK lesions and multiple AK lesions / field cancerization[113, 114], ingenol mebutate 0.05% for the treatment of lesions on the trunk or extremities was statistically significantly superior with respect to complete clearance (RR: 5.40; 95%-CI: 2.84 - 10.27; GRADE: moderate quality) and partial clearance (RR: 7.12; 95%-CI: 4.36 - 11.64; GRADE: moderate quality).

Initially, a weak recommendation was made for the use of ingenol mebutate in patients with multiple AK lesions / field cancerization, mainly due to the fact that the treatment option had been on the market for just a short period of time with limited experience on the side of the experts. Now, with 10 months of further experience the experts felt more comfortable to support a strong recommendation for this newly available treatment. The adherence to the treatment due to the short treatment regimen of 2 / 3 days is assumed to be superior to other topical interventions for AK, supplying a further argument for the use of ingenol mebutate. No recommendation was made for immunosuppressed patients due to missing data and experience concerning this patient group.

Recommendation	**Strength of recommendation**	**Percentage of agreement**
In patients with single AK lesions, we suggest using ingenol mebutate 0.015% for lesions on the face or scalp and ingenol mebutate 0.05% for lesions on the trunk or extremities.	↑	≥90%
In patients with multiple AK lesions or field cancerization, we recommend using ingenol mebutate 0.015% for lesions on the face or scalp and ingenol mebutate 0.05% for lesions on the trunk or extremities.	↑↑	≥50%*
We cannot make a recommendation with respect to ingenol mebutate for immunosuppressed patients.	0	≥90%
** Experts who did not agree voted for making a weak recommendation (↑) for the use of ingenol mebutate in patients with multiple AK lesions or field cancerization.*		

8.11. 5-aminolevulinic acid photodynamic therapy (ALA-PDT)

- Compared to placebo-PDT in samples of participants with single and multiple AK lesions or field cancerization, ALA-PDT had a statistically significantly superior efficacy concerning complete clearance (RR: 5.95; 95%-CI: 4.22 - 8.40; GRADE: low quality), partial clearance (RR: 6.77; 95%-CI: 3.91 - 11.71; GRADE: moderate quality), and the mean percent reduction of lesion counts from baseline to the end of the study (mean difference: 33.60%; 95%-CI: 18.27 - 48.93; GRADE: moderate quality).
- Compared to cryotherapy in a sample of participants with single and multiple AK lesions / field cancerization[80], ALA-PDT (red light) was statistically significantly superior with respect to complete clearance (small effect size, uncertain clinical importance; GRADE: very low quality). With respect to "skin irritation", a statistically significant higher rate of events was seen in the ALA-red light PDT group (GRADE: low quality). For details see chapter 8.2.
- Compared to CO_2 laser in an intraindividual study with a sample of participants who had single and multiple AK lesions / field cancerization[82], no statistically significant difference was seen in the participants' preference (RR: 2.0; 95%-CI: 0.94 - 4.27; GRADE: very low quality).
- Compared to 0.5% 5-fluorouracil in a sample of participants who had single and multiple AK lesions / field cancerization[95], no statistically significant differences were seen concerning complete clearance (RR: 0.58; 95%-CI: 0.25 - 1.35; GRADE: very low quality), partial clearance (RR: 0.78; 95%-CI: 0.49 - 1.24; GRADE: very low quality), withdrawals due to adverse events (RR: 0.17; 95%-CI: 0.01 - 3.96; GRADE: very low quality), improvement in global response (RR: 0.74; 95%-CI: 0.44 - 1.25; GRADE: very low quality), improvement in tactile roughness (RR: 0.92; 95%-CI: 0.52 - 1.61; GRADE: very low quality), and improvement in mottled hyperpigmentation (RR: 0.65; 95%-CI: 0.34 - 1.26; GRADE: very low quality).
- Compared to 5% imiquimod in a sample of participants who had multiple AK lesions / field cancerization[110], participants preferred ALA-PDT on a statistically significant level (RR: 2.50; 95%-CI: 1.33 - 4.70; GRADE: moderate quality). No statistically significant differences were seen with respect to the minor adverse event "erythema" (RR: 1.08; 95%-CI: 0.95 - 1.21; GRADE: moderate quality). Statistically significantly more minor adverse events occurred in the ALA-PDT treated area, with respect to "burning" (RR: 8.14; 95%-CI: 3.05 - 21.77; GRADE: moderate quality), "pain" (RR 19; 95%-CI: 4.00 - 90.34; GRADE: low quality), and "oedema" (RR: 9.50; 95%-CI: 2.44 - 37.00; GRADE: moderate quality).
- Compared to MAL-PDT in samples of participants with single and multiple AK lesions / field cancerization[115, 116], one trial[115] could demonstrate a statistically significant superiority of ALA-PDT with respect to complete clearance (RR: 1.22; 95%-CI: 1.09 - 1.37; GRADE: low quality). However, the effect is of uncertain clinical importance due to the small effect size. A small intraindividual study[116] did not show a statistically significant difference concerning complete clearance (these data could not be pooled together due to the inter- and intraindividual study design). No statistically significant differences were seen concerning mean reduction in lesions count from baseline to one month after the treatment (mean difference: 0.60; 95%-CI: -1.28 - 2.48; GRADE: low quality). Participants preferred MAL-PDT over ALA-PDT (RR: 0.2; 95%-CI: 0.05 - 0.76; GRADE: moderate quality). No statistically significant differences were seen with respect to minor adverse events and cosmetic outcomes: local skin reactions in general (RR: 1.01; 95%-CI: 0.92 - 1.10; GRADE: moderate quality); burning (RR: 0.95; 95%-CI: 0.89 - 1.02; GRADE: moderate quality); pain (RR: 0.95; 95%-CI: 0.85 -

1.06; GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "good/very good" (RR: 0.96; 95%-CI: 0.78 - 1.17; GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "unsatisfactory/impaired" (RR: 0.94; 95%-CI: 0.52 - 1.72; GRADE: low quality); and improvement in skin quality (RR: 1.00; 95%-CI: 0.99 - 1.01; GRADE: moderate quality). The intraindividual study reported higher pain scores for ALA-PDT as compared to MAL-PDT during the treatment.[116]

The weak recommendation for using ALA-PDT in immunosuppressed patients is based on indirect evidence from the efficacy data of MAL-PDT in immunosuppressed patients and clinical experience with respect to efficacy and tolerability. There is concern and debate about the possibility of an increased risk for the development of SCC in immunosuppressed patients after PDT due to a possible mutagenic potential; however, there are two papers showing no increase of the risk for SCC development after PDT.[117, 118]

Recommendation	Strength of recommendation	Percentage of agreement
We suggest using ALA-PDT in patients with single AK lesions.	↑	≥75%
We recommend using ALA-PDT in patients with multiple AK lesions or field cancerization.	↑↑	≥75%
We suggest using ALA-PDT in immunosuppressed patients with AK.	↑	≥90%

8.12. Methylaminolevulinate photodynamic therapy (MAL-PDT)

- Compared to placebo-PDT in samples of immunocompetent participants with single and multiple AK lesions or field cancerization[115, 119-123], MAL-PDT was statistically significantly superior with respect to complete clearance (RR: 4.22; 95%-CI: 3.19 - 5.59; GRADE: moderate quality) and partial clearance (RR: 3.28; 95%-CI: 1.73 - 6.23; GRADE: low quality).
- Compared to placebo-PDT in a sample of immunosuppressed organ transplant recipients[124], MAL-PDT was statistically significantly more effective concerning complete clearance (RR: 27.00; 95%-CI: 1.73 - 420.67; GRADE: low quality).
- Compared to cryotherapy in samples of participants who had single or multiple AK lesions / field cancerization[76-79], no statistically significant differences were seen concerning withdrawals due to adverse events (GRADE: very low quality), as well as with respect to the participant's rating of the cosmetic outcome as excellent or good (GRADE: low quality). For photosensitivity reaction, a lower rate was seen in the cryotherapy group, when compared to the MAL-PDT group (GRADE: very low quality). For the event 'cold exposure injury', a higher rate was seen in the cryotherapy group (GRADE: very low quality). An "excellent or good" cosmetic outcome as rated by the investigator was seen in a higher proportion of participants who were assigned to the MAL-PDT group (statistically significant difference of uncertain clinical importance due to the small effect size; GRADE: very low quality). Participants from the intraindividual split-patient trial preferred MAL-PDT over cryotherapy (GRADE: low quality) and a lower proportion of patients was satisfied with the cryotherapy (GRADE: very low quality). For details see chapter 8.2.
- Compared to 5% imiquimod in samples of participants who had multiple AK lesions / field cancerization[111, 112], there was no statistically significant difference between the

interventions concerning efficacy: complete clearance (RR: 0.37; 95%-CI: 0.12 - 1.08; GRADE: low quality) and partial clearance rates (RR: 1.30; 95%-CI: 0.92 - 1.84; GRADE: low quality). A statistically significantly higher rate of participants was "very satisfied" with MAL-PDT than with 5% imiquimod (RR: 1.49; 95%-CI: 1.21 - 1.84; GRADE: moderate quality).

- Compared to ALA-PDT in samples of participants with single and multiple AK lesions / field cancerization[115, 116], one trial[115] could demonstrate a statistically significant superiority of ALA-PDT with respect to complete clearance (GRADE: low quality). However, the effect is of uncertain clinical importance due to the small effect size. A small intraindividual study[116] did not show a statistically significant difference concerning complete clearance (these data could not be pooled together due to the inter- and intraindividual study design). No statistically significant differences were seen concerning mean reduction in lesions count from baseline to one month after the treatment (GRADE: low quality). Participants preferred MAL-PDT over ALA-PDT (GRADE: moderate quality). No statistically significant differences were seen with respect to minor adverse events and cosmetic outcomes: local skin reactions in general (GRADE: moderate quality); burning (GRADE: moderate quality); pain (GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "good/very good" (GRADE: moderate quality); the rate of participants whose cosmetic outcome was rated as "unsatisfactory/impaired" (GRADE: low quality); and improvement in skin quality (GRADE: moderate quality). The intraindividual study reported higher pain scores for ALA-PDT as compared to MAL-PDT during the treatment.[116]

There is concern and debate about the possibility of an increased risk for the development of SCC in immunosuppressed patients after PDT due to a possible mutagenic potential; however, there are two papers showing no increase of the risk for SCC development after PDT.[117, 118]

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using MAL-PDT in patients with single AK lesions.	↑	≥75%
We recommend using MAL-PDT in patients with multiple AK lesions or field cancerization.	↑↑	≥75%
We suggest using MAL-PDT in immunosuppressed patients with AK.	↑	≥75%

8.13. 0.5% 5-fluorouracil + 10% salicylic acid

- Compared to its vehicle in a sample of participants with single AK lesions and multiple AK lesions / field cancerization[90], 0.5% 5-fluorouracil in combination with 10% salicylic acid was statistically significantly more effective with respect to complete clearance (RR: 3.80; 95%-CI: 2.30 - 6.27; GRADE: low quality), the rate of physician's global assessment as "good/very good" (RR: 1.68; 95%-CI: 1.39 - 2.03; GRADE: low quality) and the rate of participant's global assessment of the clinical improvement as "good/very good" (RR: 1.40; 95%-CI: 1.20 - 1.62; GRADE: very low quality).
- Compared to 3% diclofenac in 2.5% hyaluronic acid in a sample of participants with single AK lesions and multiple AK lesions / field cancerization[90], 0.5% 5-fluorouracil in

combination with 10% salicylic acid was statistically significantly more effective with respect to the rate of complete clearance (RR: 1.72; 95%-CI: 1.34 - 2.20; GRADE: low quality), the rate of participant's global assessment as "good/very good" (RR: 1.14; 95%-CI: 1.05 - 1.24; GRADE: very low quality) and the rate of physician's global assessment of the clinical improvement as "good/very good" (RR: 1.25; 95%-CI: 1.13 - 1.38; GRADE: very low quality). In the 0.5% 5-fluorouracil in combination with 10% salicylic acid group, a statistically significantly higher rate of minor adverse events with respect to application-site irritation (RR: 2.24; 95%-CI: 1.85 - 2.72; GRADE: low quality), treatment emergent adverse events (RR: 1.24; 95%-CI: 1.14 - 1.35; GRADE: very low quality) and administration site reaction (RR: 1.47; 95%-CI: 1.30 - 1.65; GRADE: low quality) was seen. No statistically significant difference with respect to the rate of infections and infestations was seen (RR: 0.99; 95%-CI: 0.54 - 1.81; GRADE: very low quality).

Recommendation	**Strength of recommendation**	**Percentage of agreement**
We suggest using 0.5% 5-fluorouracil + 10% salicylic acid for discrete, hyperkeratotic lesions in patients with single AK lesions.*	↑	≥75%
We suggest using 0.5% 5-fluorouracil + 10% salicylic acid for discrete, hyperkeratotic lesions in patients with multiple AK lesions or field cancerization.*	↑	≥90%
We cannot make a recommendation with respect to 0.5% 5-fluorouracil + 10% salicylic acid for immunosuppressed patients.	0	≥75%
* To become effective, most of the treatments need to penetrate properly into the skin. Penetration can be hindered by strong hyperkeratosis and measures to remove the hyperkeratosis may be necessary. Due to the combination with salicylic acid, this treatment is particularly deemed appropriate for the treatment of discrete hyperkeratotic AK.		

9. Combination of interventions

Martin / Correia

Pivotal clinical trials designed to gain government agency approval of a new field therapy employ study protocols whose endpoints maximize efficacy and minimize adverse effects. The adoption by dermatologists of these protocols has been met with some level of resistance due to the inconvenience of prolonged adverse effects, socially unacceptable appearance that can last weeks to months, patient compliance issues and physician reluctance to prescribe field therapies. Following a drug's approval and its widespread availability, dermatologists commonly recommend a modified protocol in an effort to enhance patient compliance, decrease adverse effects and maintain or enhance efficacy. In addition to modifying approved dosing regimens, field therapies have been combined or used sequentially with each other as well as with lesion targeted therapies with the belief that the synergistic effects of the combined mechanisms of action would improve the results. Investigator initiated clinical studies evaluating the safety and efficacy of combining therapies, because of the lack of financial resources, are generally small in size, less well designed and lack the completeness of a corporately funded pivotal trial. The majority of studies that employ modified, combination or sequential regimens are non-randomized, unblinded and/or uncontrolled, retrospective or anecdotal experiences. Although these clinical studies lack the "gold standard" of a randomized, double-blinded, placebo controlled, numerically well powered study, there is a great deal of practical information to be gained from them.

Cryotherapy, the most widely and frequently used treatment for AKs, is not an effective field therapy for broad areas containing both clinical and subclinical AKs. The rationale for the use of a field therapy in combination or sequentially with cryotherapy reflects this understanding. Vehicle controlled studies combining cryotherapy with either 5-fluorouracil, 3.75% or 5% imiquimod and 0.015% ingenol mebutate[125] demonstrate enhanced AK field clearance over cryotherapy alone. The heterogeneous nature of treatment protocols, drug concentrations and dosing regimens made study outcome comparisons impossible.

Efforts to enhance drug delivery into actinically damaged skin prompted the study of pretreatment using topical retinoids and lasers. Pretreatments utilizing tretinoin before 5-FU therapy and tazarotene prior to 5-aminolevulinic acid PDT (5-ALA PDT) failed to demonstrate enhanced field therapy efficacy. Pretreatment with a fractionated ablative CO2 laser prior to MAL PDT resulted in enhanced efficacy compared to MAL PDT alone.[126]

The sequential use of field therapies possessing differing mechanisms of action whose synergistic effects could potentially lead to an enhanced result has also been studied. Methylaminolevulinic acid PDT (MAL PDT), a broad area selectively destructive field therapy, was coupled with the immunomodulation effects of 5% imiquimod. Using approved monotherapy treatment protocols, the sequential use of MAL PDT followed by 5% imiquimod was more effective than MAL PDT alone but not 5% imiquimod alone. This result suggests a larger contribution of 5% imiquimod to their combined therapeutic efficacy. The approved protocol for ALA PDT included a 14-18hour drug incubation prior to light activation. Because of the impractical nature of this protocol, incubation times have been shortened to 1 – 3 hours resulting in decreased efficacy when compared to the approved protocol (Data on file at DUSA Pharmaceuticals, Inc. A Sun Pharma Company). Efforts to combine 5% imiquimod sequentially after ALA PDT failed to demonstrate improved efficacy in clearing 100% of the field over ALA PDT alone but did result in a statistically significant reduction in the median AK lesion count. Sequential application of PDT and imiquimod apparently gives a significantly better clinical and histologic response in the treatment of AK than PDT or imiquimod monotherapy. It also produces less intense local reactions and better tolerance

than imiquimod monotherapy.[112] In uncontrolled studies, pretreating with 5-FU prior to ALA PDT;[127, 128] and combining 5-FU with chemical peels[129, 130] resulted in improved AK clearance.

Treating AKs on the extremities, particularly the hands, has been more resistant to field therapies than treating face/scalp AKs. The use of 3% diclofenac gel prior to ALA PDT to the hands resulted in a significant individual lesion reduction compared to ALA PDT alone[131]. An uncontrolled study combining a daily regimen of 5% imiquimod in the morning and 5% 5-FU in the evening for one week/month for 3 monthly cycles resulted in a significant reduction in AKs on the hands.[132]

Chemical peels provide an effective and low cost field therapy for both visible and subclincial AKs in addition to improving cosmesis. Isolated medium-depth chemical peeling[133, 134] or sequential cryotherapy and medium-depth chemical peeling were previously reported in poorly controlled studies. Side effects include hypopigmentation, hyperpigmentation and the potential for scarring depending on the depth of the peel. Variations in the type of chemical peel and user technique make evidence based analysis of this approach difficult.

Based on the evidence supporting the efficacy and safety of available therapies it is recognized that no single treatment or combination of modalities is optimal. There is a wide range of factors affecting a physician's choice of treatment. These include the location and characteristics of the actinically damaged skin, commercial availability of a given treatment, patient preference, treatment compliance issues, the health of the patient and financial coverage for treatments by health care systems. Taking into account these factors, continued efforts to develop new and novel approaches to the treatment of AKs will hopefully provide solutions to the increasing burden of AKs on healthcare systems.

10. Photoprotection

Lim / Werner

Protection from sunlight is an integral part of management of patients with AK. There are three components to photoprotection: behavioral modification by seeking shade during the peak UVB hours of 10AM to 2PM, wearing photoprotective outfit (including clothing, wide-brimmed hat and sunglasses) and application of broad spectrum sunscreens with SPF 30 or above. When available, UV index (low: 1-2, to extreme, 11+) can be used as a guide of photoprotection.

The beneficial effect of regular sunscreen application on a daily basis was demonstrated in various clinical trials: several trials provided evidence for a reduced incidence of new AK and a reduction of the total AK lesions count in the groups assigned to regular sunscreen application.[60, 135-137] Furthermore, in one randomised trial, a reduced incidence of SCC in the group assigned to daily sunscreen use was shown during the course of the 4.5 year study[138] and during the 8 year follow-up, as compared to control, discretionary sunscreen use group.[139]

11. Limitations, implications and future directions

From the methodological point of view, there were limitations with respect to the evidence assessment as described by Gupta et al.:[7] data from intraindividual (split-patient) studies could not be pooled with data from interindividual studies due to statistical reasons. Therefore data from intraindividual studies were not included in the meta-analyses and reported separately. For continuous data such as the mean reduction in AK lesions counts, an analysis could only be performed if studies reported mean values and standard deviation. No attempts were made to impute standard deviations from other comparisons. Without standard deviation, data were not included in the systematic review because the statistical significance of differences could not be calculated. This led to exclusion of data from several studies. Furthermore, tests for publication bias could not be performed due to the limited number of studies contributing to each comparison. Studies often included a mixed sample of participants from the different predefined patient subgroups so that quality ratings concerning directness of the data had to be adapted. During the categorization of the studies with respect to study populations, studies that did not specify the enrolment of immunosuppressed patients were considered as enrolling immunocompetent participants, even though some of these studies did not contain immunosuppression as an exclusion criterion.

The consensus conference was performed as an online conference. Using a questionnaire, participants were asked for their experiences during the conference. One participant reported problems with the online access during a period of the conference, impeding his participation. No further relevant problems were reported.[140]

Due to possible efficacy and safety differences, patients with concomitant conditions of immunosuppression were assessed separately. This led to a very limited amount of available data for this patient subgroup. More trials assessing the efficacy and safety of interventions in immunosuppressed patients who have AK are needed. Similarly, data for patients with single AK lesions were very limited and the majority of recommendations for this population is therefore based on expert consensus and indirect evidence from data on patients with multiple AK lesions.

Participant's self-reported outcomes, such as the quality of life, are an increasingly significant concept of efficacy measures in dermatological studies.[141] The number of studies reporting on patient-reported outcomes that were included in this review was very limited. For further research within the field of AK treatment, patient-reported outcomes as part of the primary outcomes should be assessed. Particularly, an increased use of quality of life instruments – generic and/ or specific – is desirable. Recently, an instrument specific for patients affected by AK, the 'Actinic Keratosis Quality of Life Questonnaire (AKQoL)' has been developed.[142]

Furthermore, the need for research including long-term efficacy data must be emphasized. Efficacy outcomes included in the systematic literature assessment were limited to six months after treatment to ensure comparability. This time frame was chosen by the expert panel because of the limited number of studies assessing long-term efficacy (e.g. one or two year clearance rates). Studies assessing the long-term efficacy of the different interventions are highly desirable.

12. References

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