Guidelines of care for the management of actinic keratosis

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Background: Actinic keratoses (AK) are rough scaly patches that arise on chronically ultraviolet-exposed skin and can progress to keratinocyte carcinoma.

Objective: This analysis examined the literature related to the management of AK to provide evidence-based recommendations for treatment. Grading, histologic classification, natural history, risk of progression, and dermatologic surveillance of AKs are also discussed.

Methods: A multidisciplinary Work Group conducted a systematic review to address 5 clinical questions on the management of AKs and applied the Grading of Recommendations, Assessment, Development, and Evaluation approach for assessing the certainty of the evidence and formulating and grading clinical recommendations. Graded recommendations were voted on to achieve consensus.

Results: Analysis of the evidence resulted in 18 recommendations.

Limitations: This analysis is based on the best available evidence at the time it was conducted. The pragmatic decision to limit the literature review to English language randomized trials may have excluded data published in other languages or limited identification of relevant long-term follow-up data.

Conclusions: Strong recommendations are made for using ultraviolet protection, topical imiquimod, topical 5-fluorouracil, and cryosurgery. Conditional recommendations are made for the use of photodynamic therapy and diclofenac for the treatment of AK, both individually and as part of combination therapy regimens. (J Am Acad Dermatol 2021;XX;XXX.)

Key words: actinic keratosis; actinic keratosis guidelines; clinical guidelines for actinic keratosis; cryosurgery; dermatology; photodynamic therapy; topical agents.
CONFLICT OF INTEREST STATEMENT

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies’ Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The information below represents the authors’ disclosed relationship with industry during guideline development. Authors (listed alphabetically) with relevant conflicts with respect to this guideline are noted with an asterisk (*). In accordance with AAD policy, a minimum 51% of Work Group members did not have any relevant conflicts of interest.

Participation in 1 or more of the listed activities below constitutes a relevant conflict:

- Service as a member of a speaker bureau, consultant, advisory board, for pharmaceutical companies on actinic keratosis or actinic keratosis drugs in development or FDA approved
- Sponsored research funding or investigator-initiated studies with partial/full funding from pharmaceutical companies on actinic keratosis or actinic keratosis drugs in development or FDA approved

If a potential conflict was noted, the Work Group member recused themselves from the discussion and drafting of recommendations pertinent to the topic area of interest. Complete group consensus was obtained for draft recommendations. Areas where complete consensus was not achieved are shown transparently in the guideline.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

Actinic keratosis (AK) is one of the most common conditions diagnosed and treated by dermatologists in the United States (US). These guidelines address the management of AK from the perspective of US dermatologists, other practitioners who treat AK, and patients. Premalignant neoplasia on nonkeratinizing epithelium, such as actinic cheilitis, is not addressed.

Various AK treatments, including topical agents, cryosurgery, and photodynamic therapy (PDT), are considered. Clinical characteristics, histologic classification, natural history, risk of progression, and dermatologic surveillance of AKs are discussed.

Because treatment of AK is likely to be an ongoing process for most patients, and one that is usually accompanied by some level of discomfort, the choice of optimal therapy will ideally involve shared decision-making between the clinician and the patient.

METHODS

A multidisciplinary Work Group conducted a systematic review to address 5 clinical questions (Table I) on the management of AKs and applied the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach for assessing the certainty of the evidence and formulating and grading clinical recommendations. Efficacy was considered the performance of an intervention under ideal and controlled circumstances, whereas effectiveness was considered its
performance in real-world conditions. The strength of each recommendation and the supporting evidence are detailed in Table II. For the detailed methodology, see Appendix 1.

DEFINITION
Actinic keratoses are keratinocyte neoplasms occurring on skin that has had long-term exposure to ultraviolet radiation.

BACKGROUND
Clinical characteristics
The classic description of AKs is that of a rough scaly papule on an erythematous base that develops in anatomic areas of high ultraviolet (UV) exposure. Clinically, however, AKs can have distinct presentations, including variants. The amount of adherent scale can alter the appearance of AKs, with thicker amounts of epidermal hyperkeratosis usually associated with increased visibility and roughness. AK variants include those that range in appearance from atrophic to profoundly hypertrophic (or hyperkeratotic), including those that develop cutaneous horns. AKs also can be pigmented or Bowenoid in appearance. Clinically, AKs can be graded as mild to severe, according to the 3-level Olsen scale (Supplemental e-Appendix 2; available via Mendeley at https://doi.org/10.17632/vw48xpmz2j.2). Although this scale has been used for research purposes, grading AKs is not part of the typical workflow for most clinicians.

Histologic classification
Histologically, AKs are characterized by epidermal hyperplasia with degrees of cellular atypia that approach those of squamous cell carcinoma (SCC) in situ but stop short of full-thickness epidermal atypia. Variable amounts of inflammation accompany AKs and this is reflected in the varying degrees of patient-reported sensitivity, from no perceived discomfort to extreme sensitivity. Pain can be associated with AKs but it is also a symptom of SCC; therefore, tender AKs should be assessed carefully. Molecular data on AK development suggest that many of the cellular changes within AKs are also present within SCCs, supporting their classification as a premalignant or precancerous process along the keratinocyte carcinogenesis spectrum.

Although a biopsy is usually not needed to make a diagnosis of AK, histopathology can provide an assessment of severity. Histologic classification of AK is focused on the similarity between AKs and SCCs (Supplemental e-Appendix 2). Additional classification systems that also assess both clinical and histologic characteristics or dermatoscopic findings are also available (Supplemental e-Appendix 2). There currently is no validated gold-standard classification system, and correlation

### Table I. Clinical questions and scope

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Adults (≥18 years of age) with a clinical or histopathologic diagnosis of AK*</td>
<td>Individuals with actinic cheilitis</td>
</tr>
<tr>
<td>Intervention</td>
<td>Available standard treatments, approved, and regularly used in clinical practice in the US</td>
<td>Treatments not available or approved for use in clinical practice in the US</td>
</tr>
<tr>
<td>Study Design</td>
<td>RCTs in which study participants are investigated (inter-individual, parallel-arm trials)</td>
<td>Observational studies, retrospective studies, case series, case reports</td>
</tr>
</tbody>
</table>

AK, Actinic keratosis; RCT, randomized controlled trial; US, United States.
*Including immunosuppressed patients or organ transplant recipients for clinical question 5.
studies have led to calls for adjustments to available systems (Supplemental e-Appendix 2).20-22

Natural history and malignant progression

AKs are typically absent in the first decades of life unless genetic or environmental factors predispose an individual to increased skin damage from UV exposure. AKs typically present in areas of highest solar damage in fair-skinned individuals and have a propensity for the head, ears, neck, dorsal aspects of the arms and hands, and the lower extremities, due to their greater exposure to the sun over time.23-25 The scalp, particularly in areas of hair loss, is also a frequent site for the involvement of AKs.

Although they often persist as chronic skin lesions, AKs can spontaneously involute or, most importantly, evolve into keratinocyte carcinoma if left untreated.20-22 This is particularly concerning in patients with a previous history of skin cancer, advanced age, or other factors that predispose them to a higher rate of individual lesion progression to cancer, such as immunosuppression. Thus, AKs represent an indication for risk of developing skin cancer and are a clear target for skin cancer prevention, as the successful treatment of AKs is associated with a lower incidence of skin cancer.33

At a molecular level, the keratinocyte hyperplasia of AKs is driven by acquired somatic mutations in the keratinocyte DNA, induced by UV mutagenesis.28 The “fingerprints” of DNA mutations contained within AKs include C to T and CC to TT changes, which are seen classically in association with direct DNA damage from UVB but also in mutations in a spectrum that is more likely to be initiated by the results of reactive oxygen species triggered by endogenous aging of cells or due to UVA-induced reactive oxygen species production.34,35 The specific DNA mutations that have been characterized in AKs include those seen in keratinocyte carcinoma, including mutations in TP53, the gene encoding the p53 protein, known to have an important role in tumor suppression for a variety of malignancies, including SCC.36,37 Additional mutations that are thought to be

Table II. Strength of recommendations and supporting evidence: Wording and implications

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Wording</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation for</td>
<td>“We recommend…”</td>
<td>Benefits clearly outweigh risk and burdens; recommendation applies to most patients in most circumstances.</td>
</tr>
<tr>
<td>the use of an intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional recommendation</td>
<td>“We conditionally recommend…”</td>
<td>Benefits closely balanced with risks and burden; recommendation applies to most patients, but most appropriate action may differ, depending on the patient or other stakeholder values.</td>
</tr>
<tr>
<td>for the use of an intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong recommendation against</td>
<td>“We recommend against…”</td>
<td>Risk and burden clearly outweigh benefits; recommendation applies to most patients in most circumstances.</td>
</tr>
<tr>
<td>the use of an intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditional recommendation against</td>
<td>“We conditionally recommend against…”</td>
<td>Risks and burden closely balance with benefits; recommendation applies to most patients, but most appropriate action may differ, depending on the patient or other stakeholder values.</td>
</tr>
<tr>
<td>the use of an intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good Practice Statement</td>
<td>“We recommend…”</td>
<td>Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect and the certainty surrounding an intervention’s impact was high, with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations, as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Wording</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>“high quality evidence”</td>
<td>Very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>“moderate quality evidence”</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>“low quality evidence”</td>
<td>Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>“very low quality evidence”</td>
<td>The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>
pathogenic in the development of AK include mutations in p16, ras family members, NFKB, CDKN2A, telomerase, and TNF alpha.\textsuperscript{38-43}

Estimates of the risk of progression of AK to SCC vary from less than 0.1% to 20%.\textsuperscript{27,30,44,45} Limited follow-up in many studies makes precise AK prognosis difficult. Studies that have examined SCC histologically to look for adjacent contiguous AK have reported the finding in more than 60% of cases.\textsuperscript{29,32} The spontaneous regression rate of AKs is highly variable and has been reported to be from 15% to 63% per year.\textsuperscript{44,45} AKs that spontaneously regress clinically have been reported to recur, with a recurrence rate estimated to be as high as 50% within the first year.\textsuperscript{15}

**MANAGEMENT**

Treatment options available for AKs include topically applied creams, gels, and solutions; cryosurgery; and PDT. The selection of treatment is based on AK features (eg, site), treatment-related factors (eg, efficacy, tolerability, and burden), and patient characteristics and preferences. The primary patient-focused considerations for the treatment of AKs are the associated symptoms, the risk of progression to keratinocyte carcinoma, tolerability, burden of treatment, and the cosmetic appearance of the AKs before, during, and after treatment.\textsuperscript{46}

Although these guidelines are focused on the treatment of AKs, there are some situations in which nontreatment is a potential option. For patients with limited life expectancy or for whom the morbidity of treatment outweighs the potential benefits, observation may be considered.\textsuperscript{27,44,47}

Because the degree of patient participation and range of discomfort can vary between treatment modalities, it is important that the patient and the treating clinician share decision-making about the choice of therapy. These decisions will ultimately balance the patient’s compliance habits, ability to tolerate anticipated local skin reactions or discomfort, preferred duration of therapy, and health outcomes with the provider’s assessment of the predicted likelihood of achieving a successful outcome.

Treatment of AK can be field directed or lesion directed. Field directed treatments, such as topical agents or PDT, can be used to manage multiple AKs and keratinocyte changes in a contiguous area and may provide benefits in reducing the risk of developing new AKs, limiting AK recurrence, and mitigating subclinical damage.\textsuperscript{48} Lesion-directed treatments are used to manage few or isolated AKs. Treating individual AKs in the office setting with physical modalities such as liquid nitrogen cryosurgery or destructive modalities such as curettage offers the patient a treatment that is completed within a single visit and requires only that the patient participate in post-procedural skincare. There are practical limitations to the absolute number of individual AK lesions that can be treated in this manner before patient discomfort, potential adverse events, and clinician time may make a field directed treatment a better option.

**UV protection**

Randomized controlled trials (RCTs) have demonstrated that the use of sunscreen to prevent UV exposure is associated with a small reduction in the incidence of AK and in the development of new AKs.\textsuperscript{49,50} A study comparing the application of a vehicle cream or sunscreen (sun protection factor of 17) for 6 months found sunscreen users had fewer new AKs (rate ratio 0.62; 95% confidence interval [CI], 0.54-0.71) and greater odds of remission of baseline AKs (odds ratio [OR] 1.53; 95% CI, 1.29-1.80).\textsuperscript{49} Similarly, it is reported that the ratio of AK counts was lower in individuals randomized to daily sunscreen use (1.20; 95% CI, 1.04-1.39) than in individuals randomized to discretionary sunscreen use (1.57; 95% CI, 1.35-1.84) over a 2-year follow-up period. These findings suggest a 24% reduction in AK counts with the use of sunscreen.\textsuperscript{50} The Work Group strongly recommends as a measure of good practice that patients with AKs minimize their exposure to UV (Table III). It is recommended that this avoidance be multifaceted, including avoiding exposure to both natural and artificial sources of UV and the use of sun-protective clothing and sunscreen that can block both UVA and UVB.

**Topical agents**

The use of topically applied creams, gels, and solutions for the management of AK is common in dermatology practice. Topical agents can be used focally or in broad areas and are particularly advantageous when AKs occur in areas of high density or areas with indistinct clinical borders. The recommended topical agents all have the potential for generating local skin reactions. As skin reactions can result in the termination of treatment without reaching the desired therapeutic outcome, the clinician is charged with working with the patient to tailor an individual treatment program that achieves the desired results.

The literature on AK treatment supports a strong recommendation for field treatment with either 5-fluorouracil (5-FU) or imiquimod (Table III). Due to the various commercial preparations of these drugs, the treatment regimens studied often vary in
terms of the concentration, dosing interval, and duration (Table IV). The Work Group conditionally recommends the use of diclofenac, based on lower quality of evidence than that of the evidence supporting strong recommendations for the use of 5-FU or imiquimod (Table III).

**Fluorouracil**

The benefits of 5-FU treatment for AK were assessed as moderate or large, based on moderate-to-high quality efficacy data from 5 identified studies (Table IV). Local irritation was the primary source of harm to patients and often the primary reason for the discontinuation of treatment. The overall assessment of the level of harm from 5-FU was small and based on data of moderate quality. The Work Group considered there to be potential variability in the value patients placed on AK clearance, considering side effects, such as irritation, which could affect treatment selection and adherence. All of the evaluated studies assessed field treatment with 5-FU. Thus, the Work Group recommends the use of topical 5-FU as a field treatment for AKs.

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**Table III. Recommendations for management of actinic keratosis**

<table>
<thead>
<tr>
<th>No.</th>
<th>Recommendation</th>
<th>Strength</th>
<th>Quality of evidence</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UV protection</td>
<td>For patients with AK, we recommend the use of UV protection</td>
<td>Strong</td>
<td>Good Practice Statement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remarks: UV protection may include sun avoidance, sun-protective clothing, and broad-spectrum sunscreen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical agents</td>
<td>For patients with AKs, we recommend field treatment with 5-fluorouracil</td>
<td>Strong</td>
<td>Moderate 52-56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we recommend field treatment with imiquimod</td>
<td>Strong</td>
<td>Moderate 58-69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend the use of diclofenac</td>
<td>Conditional</td>
<td>Low 80-83</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remarks: As with other oral and topical medications in the class, NSAIDs carry a black box warning for cardiovascular and gastrointestinal side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryosurgery</td>
<td>For patients with AKs, we recommend the use of cryosurgery</td>
<td>Strong</td>
<td>Good Practice Statement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend treatment with cryosurgery over CO2 laser ablation</td>
<td>Conditional</td>
<td>Moderate 99</td>
<td></td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>For patients with AKs, we conditionally recommend ALA-red light PDT</td>
<td>Conditional</td>
<td>Low 116-119</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend 1 to 4-hour 5-ALA incubation time to enhance complete clearance with red light PDT</td>
<td>Conditional</td>
<td>Low 121</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend ALA-daylight PDT as less painful than but equally effective as ALA-red light PDT</td>
<td>Conditional</td>
<td>Moderate 122</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend treatment with ALA-red light PDT over trichloroacetic acid peel</td>
<td>Conditional</td>
<td>Moderate 123</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend ALA-blue light PDT</td>
<td>Conditional</td>
<td>Moderate 100,124-126</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend against pretreatment with alpha hydroxy acid solution prior to ALA-blue light PDT</td>
<td>Conditional</td>
<td>Very Low 130</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend treatment with ALA-red light PDT over cryosurgery alone</td>
<td>Conditional</td>
<td>Low 131</td>
<td></td>
</tr>
<tr>
<td>Combination therapy</td>
<td>For patients with AKs, we conditionally recommend the combined use of 5-FU and cryosurgery over cryosurgery alone</td>
<td>Conditional</td>
<td>Moderate 55,132</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend the combined use of imiquimod and cryosurgery over cryosurgery alone</td>
<td>Conditional</td>
<td>Low 64,133,134</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend against the use of diclofenac in addition to cryosurgery compared to cryosurgery alone</td>
<td>Conditional</td>
<td>Low 135</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend against the use of topical adapalene in addition to cryosurgery compared to cryosurgery alone</td>
<td>Conditional</td>
<td>Low 136</td>
<td></td>
</tr>
<tr>
<td></td>
<td>For patients with AKs, we conditionally recommend against the addition of imiquimod following ALA-blue light PDT</td>
<td>Conditional</td>
<td>Moderate 137</td>
<td></td>
</tr>
</tbody>
</table>

AK, Actinic keratosis; ALA, aminolevulinic acid; CO2, carbon dioxide; FU, fluorouracil; NSAID, nonsteroidal anti-inflammatory drug; No, Number; PDT, photodynamic therapy; UV, ultraviolet.
A large, placebo-controlled randomized trial showed field treatment of AKs on the face with 5% 5-FU treatment twice daily for 4 weeks to be more effective than placebo for complete AK clearance at 6 months (38% vs 17%, respectively; \( P < .01 \); Supplemental e-Table 1a). Four placebo-controlled RCTs evaluated the efficacy and safety of 0.5% 5-FU, suggesting the lower concentration of 5-FU to be more effective than placebo for complete clearance of AKs (Supplemental e-Table 1b). Two of the studies provided data on skin irritation, suggesting that more than 90% of patients treated with 0.5% 5-FU/salicylic acid experience irritation.

Fluorouracil combined with calcipotriene

An emergent topical treatment for AKs is the combination of 5-FU with calcipotriene (calcipotriol). The systematic review identified an RCT of 131 patients that compared the efficacy and safety of 5% 5-FU combined with 0.005% calcipotriol ointment to that of 5% 5-FU combined with vehicle applied twice daily for 4 consecutive days for the field treatment of AKs on the face, scalp, and upper extremities. Although outside the scope of the present guidelines, which are focused on currently available treatment options, the Work Group considered the evidence to be of note. Specifically, application of 5-FU combined with calcipotriol compared to 5-FU combined with vehicle resulted in a mean reduction in the number of AKs of 87.8% and 26.3% on the face, 76.4% and 5.7% on the scalp, 68.8% and 9.6% on the right upper extremity, and 79% and 16.3% on the left upper extremity, respectively (\( P < .0001 \) for all anatomic sites).

These findings suggest that the greater efficacy of the combination therapy remained significant after controlling for age, sex, and baseline AK count (\( P < .0001 \) for all anatomic sites). Complete clearance data also suggest greater efficacy with the combined use of 5-FU and calcipotriol, with 27% of participants in the combination therapy group reporting complete clearance of AKs on the face compared to 0% of participants in the 5-FU and vehicle group.

### Table IV. Topical agents study characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Anatomic location</th>
<th>Treatment type</th>
<th>Vehicle</th>
<th>Concentration (%</th>
<th>No. of doses</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorizzo 2002</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>0.5</td>
<td>1/d</td>
<td>7, 14, or 28 d</td>
</tr>
<tr>
<td>Jorizzo 2004</td>
<td>Face</td>
<td>Field</td>
<td>Cream</td>
<td>0.5</td>
<td>1/d</td>
<td>7 d</td>
</tr>
<tr>
<td>Jorizzo 2006</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>0.5</td>
<td>1/d</td>
<td>7 d</td>
</tr>
<tr>
<td>Pomerantz 2015</td>
<td>Face</td>
<td>Field</td>
<td>Cream</td>
<td>5</td>
<td>2/d</td>
<td>28 d</td>
</tr>
<tr>
<td>Weiss 2002</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>0.5</td>
<td>1/d</td>
<td>7, 14, or 28 d</td>
</tr>
<tr>
<td>Alomar 2007</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>5</td>
<td>3/wk</td>
<td>4 or 8 wks (1 or 2 courses)</td>
</tr>
<tr>
<td>Chen 2003</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>5</td>
<td>3/wk</td>
<td>3 or 6 wks (2 courses)</td>
</tr>
<tr>
<td>Gebauer 2009</td>
<td>Arms or hands</td>
<td>Field</td>
<td>Cream</td>
<td>5</td>
<td>2,3,5,</td>
<td>8 wks</td>
</tr>
<tr>
<td>Hanke 2010</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>2.5 or 3.75</td>
<td>7/wk</td>
<td>6 wks (3 on, 3 off, 3 on)</td>
</tr>
<tr>
<td>Hanke 2011</td>
<td>Face or scalp</td>
<td>Field</td>
<td>Cream</td>
<td>2.5 or 3.75</td>
<td>7/wk</td>
<td>4 wks (2 on, 2 off, 2 on) or 6 (3 on, 3 off, 3 on)</td>
</tr>
<tr>
<td>Jorizzo 2007</td>
<td>Head</td>
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*HA, hyaluronic acid; No, number; wk, week.*
(P < .0001). The higher efficacy of 5-FU combined with calcipotriol was associated with significantly higher percentages of participants reporting skin redness (69% vs 25%, P < .0001) and burning (39% vs 13%, P = .0008) but not scaling (14% vs 7%, P = .22) or itching (25% vs 22%, P = .75) during the 4-day treatment period. Further confirmatory studies are needed to provide sufficient evidence of the efficacy and safety of 5-FU combined with calcipotriene to manage AK.

**Imiquimod**

Topical application of imiquimod in various concentrations over a range of application frequencies showed moderate to large benefits for the management of AK in various anatomic locations (Table IV). Harms primarily consisted of localized skin irritation or influenza-like symptoms. The efficacy and harms data were of moderate to high quality. Thus, the Work Group recommends field treatment with topical imiquimod for management of AKs.

The systematic review identified 12 placebo-controlled, randomized trials of the efficacy and safety of imiquimod for the treatment of AKs (Table IV).58-69 Studied in concentrations of 5%, 3.75%, and 2.5%, most data on the efficacy of topical imiquimod for the management of AKs were derived from 8 RCTs studying 5% imiquimod cream applied 2 to 3 times a week for 1 to 2 treatment courses. These 8 trials reported complete clearance rates of between 3.2% and 55% (average 29.3%) for 9 to 24 doses and between 3.3% and 84% (average 40.8%) for 32 to 56 doses (Supplemental e-Table 2a).58-60,63,65-67,69 These studies report adverse effects of treatment including local skin reactions in up to 98% of patients, influenza-like symptoms in 3.2% to 10.3% of patients, and infection in 1.6% to 2.3% of patients (Supplemental e-Tables 2b and 2c). A subset of the studies on 12 to 56 doses of 5% imiquimod report participant rates of discontinuation of treatment due to adverse events ranging from 1.6% to 33.3% (average 12.6%; Supplemental e-Table 2d).

Four placebo-controlled studies provided data on the efficacy of 3.75% imiquimod cream for the treatment of AKs on the face and scalp (Supplemental e-Table 2e).61,62,64,68 A study of 3.75% imiquimod applied daily for two 2-week periods separated by 2 weeks off treatment reports that at 17 weeks the post treatment rates of complete clearance were 34% and 5.5% for imiquimod and placebo-treated patients, respectively (risk ratio [RR] 6.19; 95% CI, 3.16-12.10; P < .0001).61 Similarly, a study of 3.75% imiquimod applied daily for two 2-week periods separated by 2 weeks off treatment showed complete clearance rates of 35.6% for imiquimod-treated patients and 6.3% for vehicle-treated patients at 14 weeks (RR 5.66; 95% CI, 3.00-10.69; P < .0001).63 A complete clearance rate of 59.5% is reported for treatment with 3.75% imiquimod once daily for two 2-week periods separated by a 2-week off treatment period following cryosurgery.64 Long-term data suggest that at 14 months, AKs that responded to 3.75% imiquimod treatment recurred in 60% of patients.65 With 3.75% imiquimod, severe local skin reactions were reported at 14 to 17 weeks follow up in 33.8% of patients receiving 28 doses and 54.9% of patients receiving 42 doses (Supplemental e-Table 2f).61,62,68 Influenza-like illness with 42 doses of 3.75% imiquimod was reported in 8% of patients at 17 weeks (Supplemental e-Table 2g).61 Discontinuation of treatment with 3.75% imiquimod due to adverse events was reported for 1.3% of patients prescribed 28 doses and 2.5% of patients prescribed 42 doses.61,68

Three studies evaluated the efficacy and safety of lower concentration 2.5% imiquimod cream for the treatment of AKs on the face and scalp (Supplemental e-Table 2h).51,62,68 Applied daily for two 2-week periods separated by 2 weeks off treatment, complete clearance rates for 2.5% imiquimod of 30.6% and 33.3% are reported at 14-week and 12-month follow-up, respectively.62,68 Studies of longer treatment courses—2.5% imiquimod applied daily for two 3-week periods separated by 3-weeks off treatment—report complete clearance rates of 25% and 43.2% at 17 weeks and 12 months, respectively.61,62 Severe local skin reactions occurred in 20.6% of patients receiving 28 doses of 2.5% imiquimod (Supplemental e-Table 2i).68 At 42 doses of imiquimod, severe local skin reactions were reported in 41.5% of patients and influenza-like illness was reported in 3.7% of patients (Supplemental e-Tables 2i and 2j).65 Discontinuation of treatment with 2.5% imiquimod due to adverse events was reported for 0.6% of patients prescribed 28 doses and 1.2% of patients prescribed 42 doses (Supplemental e-Table 2i).61,68

**Ingenol mebutate**

At the initiation of guideline development, the Work Group identified topical ingenol mebutate as an available option for the management of AKs. The systematic review identified a body of evidence concerning the efficacy and safety of topical ingenol mebutate, which was considered by the Work Group (Supplemental e-Tables 3a-3j).70-77 During the drafting period of this manuscript, market authorization for ingenol mebutate in the European Union was withdrawn. Unpublished
safety data reviewed by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee is reported to show that at 3 years the incidence of skin cancer in skin areas treated with ingenol mebutate is more than 3 times higher than that observed with imiquimod (15 of 240 [6.3%] and 5 of 244 [2%], respectively). Also, the Pharmacovigilance Risk Assessment Committee considered data on ingenol disoxate, a chemically similar but distinct compound, concluding that “the medicine may increase the risk of skin cancer and that its risks outweigh its benefits.” Following the withdrawal of market authorization in the European Union, the drug developer subsequently initiated a recall of ingenol mebutate in Canada and provided the US Food and Drug Administration (FDA) with notification of permanent discontinuation of manufacturing and marketing of the medication. Ingenol mebutate is expected to be completely removed from the market in the US by the end of 2020. As the scope of this guideline is limited to available treatment options for AK in the US, no recommendation is provided on the use of ingenol mebutate.

Diclofenac

Based on a review of studies of diclofenac gel (in a 2.5% hyaluronic acid vehicle) compared to vehicle, the benefits and potential harms, primarily local skin reactions, of diclofenac treatment were assessed as small, based on efficacy and safety data of low to moderate quality (Supplemental e-Tables 4a and 4b). Of note, use of nonsteroidal anti-inflammatory drugs, including topical diclofenac, is accompanied by a boxed warning of increased risk of cardiovascular thrombotic events as well as gastrointestinal complications, including gastrointestinal bleeding, ulceration, and perforation. This may impact treatment choice, particularly for patients who already use nonsteroidal anti-inflammatory drugs for other conditions.

Four RCTs evaluating the efficacy and safety of 3% diclofenac in 2.5% hyaluronic acid for the treatment of AKs were identified by the systematic review (Table IV). A study of twice daily diclofenac treatment for a mean of 60 days reports 33% clearance of baseline AKs in the treatment group compared to 10% in the vehicle group (P < .05). Pooled data from 2 vehicle-controlled studies of twice daily 90-day treatment with diclofenac shows 42% of treated patients achieved complete clearance compared to 14% of vehicle-treated participants (RR, 2.93; 95% CI, 1.85-4.65; P < .00001). Adverse events at the site of treatment were reported for 29% of patients using diclofenac twice daily for 24 weeks, compared to 4.7% of participants in the vehicle group (RR, 6.19; 95% CI, 1.92-19.98; P = .002). Pooled data suggest rates of discontinuation of treatment due to adverse events of 15% and 4% for diclofenac and vehicle-treated patients, respectively (RR, 3.59; 95% CI, 1.92-6.70; P < .0001).

Tirbanibulin

Topical 1% tirbanibulin ointment, a novel microtubule inhibitor, was approved for treatment of AK on the face and scalp by the FDA after completion of this analysis. Results from 2 Phase III clinical studies, representing a total of 702 participants, demonstrated that tirbanibulin 1% ointment was superior to vehicle ointment as a topical treatment for AK of the face and scalp at 2 months. Complete clearance rates were 44% compared to 5% in trial 1 and 54% compared to 13% in trial 2, respectively. Among participants with a complete response to tirbanibulin, the estimated percentage of patients with recurrent lesions at 1 year was 47%. Risks were reported to include mostly mild to moderate local reactions and no participants were reported to have been withdrawn from the trials due to adverse events.

Comparative effectiveness of topical therapies for AK

The systematic review identified a few small studies that directly compared the efficacy and safety of various topical medications to treat AK. This limited evidence was considered by the Work Group to be insufficient to form recommendations on the comparative efficacy and safety of topical therapies for AK (Supplemental e-Appendix 3). Two additional recent studies, published after completion of the systematic literature search for this analysis, have compared the efficacy of 4 field directed treatments and 2 topical agents. Supplemental e-Appendix 4 provides a summary of the evidence.

Cryosurgery

There is significant evidence from prospective studies and comparative trials to support the use of cryosurgery as a readily available, rapid, and effective lesion-directed treatment for AKs. Clinically, cryosurgery has been reported to cure between 57% and 98.8% of AKs followed up over 3 months to 8.5 years. Clearance rates have been shown to vary with duration of freeze. A prospective, multicenter study of spray cryosurgery for the treatment of AKs on the face or scalp reports complete clearance rates of 39%, 69%, and 83% for freeze times of less than 5 seconds, 5-20 seconds, and greater than 20 seconds, respectively. The Work Group strongly recommends cryosurgery as a treatment approach...
for individual AKs as good practice (Table III). Discomfort during treatment and dyschromia after treatment constitute the major risks of the procedure and these tend to be minimized with shorter freezing times, although this may also reduce the overall rate of complete responses to treatment.98

Laser ablation of AKs is another destructive therapeutic modality but it is not as widely available as cryosurgery in dermatology offices. A study that compared laser resurfacing to cryosurgery for the treatment of AKs on the face and scalp favored the outcomes of cryosurgery for both lesion reduction and complete clearance (Supplemental e-Table 5).99 At 3 months post treatment, 78.2% of baseline AKs treated with cryosurgery were cleared, compared to 72.4% of AKs treated with laser ablation (RR, 1.08; 95% CI, 0.98-1.19; \( P = .12 \)) and the incidence of complete clearance was 71.6% for cryosurgery-treated patients and 65.3% for laser-treated participants (RR, 1.10; 95% CI, 0.91-1.32; \( P = .34 \)). Although adverse effects were not examined systematically, patient satisfaction ratings also significantly favored cryosurgery over CO₂ laser. Thus, the Work Group conditionally recommends cryosurgery over CO₂ laser ablation and this recommendation is supported with moderate quality evidence (Table IV).

**Photodynamic therapy**

PDT is an attractive platform for the treatment of AKs, as it is administered in the office setting. This can improve compliance over therapies completed by patients outside of the office. PDT protocols in the US are based upon the commercial availability of a photosensitizing compound coupled with various light sources. Treatment protocols and duration vary as photosensitizing compound incubation time can range from overnight to less than an hour before the application of a light source.100-105

There is substantial literature to support the use of PDT with methyl aminolevulinate as a photosensitizing compound in the treatment of AKs as a stand-alone modality with a variety of energy sources or PDT combined with other topical agents before activation with red light.105-108 Because this compound is not available in the US, however, the Work Group excluded MAL-PDT from the consideration of AK therapies and forewent issuing recommendations.

The primary sensitizing agent for PDT protocols in the US is 5-aminolevulinic acid (ALA). To answer the question of whether ALA-red light PDT is effective for AK clearance and keratinocyte carcinoma prevention, the Work Group examined data from 4 studies using the sensitizing agent in the form of a 10% ALA gel (78 mg/g ALA nanoemulsion gel).116-119 These studies report ALA-red light PDT to be more effective than placebo-red light PDT for lesion reduction, complete AK clearance, and prevention of carcinoma development (Supplemental e-Table 6a). Pooled data from 3 studies on up to 2 ALA-red light PDT treatments show rates of baseline lesion clearance of 89.1% and 32.7% (RR 2.89; 95% CI 2.28-3.66; \( P < .00001 \)) at 12 weeks post treatment for ALA-PDT and placebo-PDT patients, respectively.116,118,119 Similarly, pooled rates of participants with complete clearance from these studies are 77.1% and 16.6% for ALA-PDT and placebo-PDT, respectively (RR, 4.61; 95% CI, 3.20-6.66; \( P < .00001 \)).

An additional study reporting the long-term follow-up of 2 placebo-controlled trials reports that following 1 or 2 PDT treatments at 12 months post treatment, 3.6% of ALA-PDT treated participants were diagnosed with skin cancer in the treatment area compared to 5.0% of participants treated with placebo-PDT (RR, 0.71; 95% CI 0.25-1.99; \( P = .52 \)).117 These findings are further supported by a network meta-analysis comparing the relative efficacy of 10 AK treatment modalities, including topical therapies and PDT, which concluded that ALA-PDT showed the highest efficacy compared to placebo to achieve complete patient clearance of AKs.120

The Work Group considered this efficacy data to represent a substantial benefit for the use of ALA-red light PDT treatment for AKs and considered the risks of skin irritation, pain, and cosmesis to represent minimal potential for harm. However, the overall summed quality of this evidence is low; thus, the Work Group conditionally recommends ALA-red light PDT as a treatment for AKs (Table III). As this recommendation is based on a review of the totality of the available evidence, low certainty in the evidence was driven by pooled outcome data on the critical outcome of complete clearance following a single ALA-PDT treatment session. Conversely, the evidence on the efficacy of up to 2 ALA-PDT treatment sessions is of moderate to high certainty, suggesting repeated treatment may be considered with a higher level of confidence (Supplemental e-Table 6a).

A single study examined the efficacy of different application times (0.5, 1, 2, or 4 hours) for the ALA-patch prior to the administration of red light at 37 J/cm² for the treatment of AKs.121 The study provided sufficient evidence to generate a recommendation. Longer incubation times resulted in higher complete clearance rates with harms that were primarily localized skin irritations (Supplemental e-Table 6b). The complete clearance rate with 0.5-hour application was 23.5% compared to a complete clearance rate of 73.5% with 4-hour application (RR, 0.32; 95%
The efficacy and safety of ALA-red light PDT were compared to those of chemical peeling using 35% trichloroacetic acid for treatment of AKs on the head. PDT treatment was found to be superior for lesion reduction (total lesion count reduction of 58% and 32%, respectively; \( P = .006 \)) and rates of complete clearance (74% and 49%, respectively; \( P = .011 \)) 12 months after the interventions (Supplemental e-Table 6d). Harms were considered small overall; however, treatment-associated pain on the Visual Analog Scale was significantly higher in the arm treated with ALA-red light PDT than in the arm treated with TCA peel (MD, 2.4; 95% CI, 1.08-3.72; \( P = .0006 \)). Additionally, the incidence of scarring in the treatment area was higher in the TCA arm compared to the PDT arm (21.4% vs 0%, respectively [RR for PDT compared to TCA, 0.08; 95% CI, 0.004-1.3; \( P = .08 \)).

Thus, the Work Group conditionally recommends ALA-red light PDT over 35% TCA peel for the management of AKs.

ALA-blue light PDT showed superior benefits over placebo-blue light PDT in terms of achieving complete clearance, partial clearance, lesion reduction, and prevention of carcinoma development (Supplemental e-Table 6e). At week 8, pooled data suggest that 82.2% of AKs treated with 1 course of ALA-blue light PDT cleared from baseline compared with 28.8% treated with placebo-blue light PDT (RR, 2.91; 95% CI, 2.23-3.80; \( P < .00001 \)). An additional study reports that 8 weeks after 1 treatment, a greater proportion of participants receiving ALA-blue light PDT achieved complete clearance and partial clearance compared to participants receiving placebo-blue light PDT (IR, 16.67; 95% CI, 2.31-120.36; \( P = .005 \)) and [RR, 8.70; 95% CI, 3.22-23.54; \( P < .0001 \)], respectively; Supplemental e-Table 6e). The proportion of patients who developed keratinocyte carcinomas in the areas treated with ALA-blue light PDT was smaller than that of patients treated with placebo-blue light PDT during the 24 weeks of follow-up (2.1% vs 6.5% [RR, 0.33; 95% CI, 0.08-1.41; \( P = .13 \)], but the difference was not statistically significant.

The harms to patients were considered minimal and were primarily erythema, edema, stinging, or burning at the treatment site. A significantly greater proportion of patients treated with ALA-blue light PDT reported stinging or burning compared to those treated with placebo-blue light PDT (88.3% vs 13.0% [RR, 6.77; 95% CI, 3.20-14.30; \( P < .0001 \)]). This analysis is supported by recently published data from an RCT comparing the treatment of AKs on the upper extremities with ALA-blue light PDT to treatment with vehicle blue light PDT. At 12 weeks, 31% of participants (42 of 135) treated with ALA-PDT had complete clearance compared to 13% (17 of 134) of participants treated with vehicle-PDT (\( P = .0001 \)).

The Work Group conditionally recommends ALA-blue light PDT as a treatment for AK, based upon this moderate quality evidence (Table III). There is some evidence that heating the skin with a heating pad during ALA treatment may improve AK reduction; however, the specific thermal parameters need to be better defined and the study repeated before a specific recommendation on warming the skin can be made.

A single study examined whether field treatment of AKs with 10% alpha hydroxy acid and ALA-blue light PDT resulted in fewer subsequent invasive skin cancers on the face of individuals with previous facial cutaneous malignancy. Patients were
treated with 10% alpha hydroxy acid solution for 2 weeks before 2 ALA-PDT treatments 14 days apart. There was no benefit in preventing carcinoma development seen with ALA-blue light PDT following 10% alpha hydroxy acid treatment compared to no treatment during 3 years of follow-up (RR, 1.01; 95% CI, 0.54-1.90; Supplemental e-Table 6f). Permanent scarring was reported in 3 of 34 (8.8%) patients treated with 10% alpha hydroxy acid and ALA-PDT. Thus, the potential for harm was assessed as outweighing the benefits of the combination treatment. The Work Group conditionally recommends against pretreatment with alpha hydroxy acid solution before ALA-blue light PDT for the treatment of AK, based on this very low quality evidence (Table III).

When liquid nitrogen cryosurgery was compared to red light PDT with 8 mg ALA patches (ALA-patch PDT) for treating mild to moderate AKs, there were moderate differences in benefit in lesion reduction and complete clearance that favored ALA-red light PDT (Supplemental e-Table 6g). At 12 weeks post treatment, significantly fewer AKs cleared from baseline following cryosurgery compared with ALA-patch PDT (76.6% vs 88.5%; P = .007). Complete clearance rate at 12 weeks was significantly lower with cryosurgery compared to ALA-patch PDT (RR, 0.79; 95% CI, 0.64-0.97; P = .02). However, skin irritation on the day of treatment and 1 day after treatment favored cryosurgery (RR, 0.27; 95% CI, 0.16-0.46; P < .0001). The Work Group placed a higher value on the clearance and reduction of AKs than the harms of skin irritation, conditionally recommending ALA-PDT over cryosurgery for the treatment of AKs, based on this low quality data (Table III).

Combination therapy

The systematic review of the evidence identified several trials of combination therapy for the treatment of AKs. These trials employ a serial approach to combination therapy in which treatment with a topical agent precedes or follows another treatment modality to maximize response.

Comparison studies evaluating the use of topical medications in combination with cryosurgery for the treatment of AKs have generated 5 recommendations, of which 3 conditionally support the use of the combined therapy and 2 favor the use of cryosurgery alone. An additional conditional recommendation against the use of combination therapy was informed by a study evaluating the sequential use of ALA-blue light PDT and topical imiquimod (Table III).

Two studies evaluated the combined use of 5-FU and cryosurgery to manage AKs. A randomized study compared a 1-week pretreatment course of 0.5% 5-FU cream with cryosurgery to the use of vehicle cream before cryosurgery. The benefits of the combined use of 0.5% 5-FU and cryosurgery were small compared to cryosurgery alone (Supplemental e-Table 7a). The magnitude of the added benefit to the combination therapy over cryosurgery alone tended to dissipate with repeated cycles of combined therapy versus cryosurgery alone. Similarly, a study randomizing participants to 0.5% 5-FU treatment for 1 week following cryosurgery reports nonsignificant improvement in the 5-FU group compared to cryosurgery alone.

These studies report nonsignificant differences in adverse events after the first combination treatment cycle (although local skin reactions worsened with subsequent treatment cycles in the 5-FU treatment group). Based on this moderate quality evidence suggesting enhanced lesion reduction without increased adverse events, combined 5-FU cream and cryosurgery is conditionally recommended over cryosurgery alone. Studies have compared the use of imiquimod in 3.75% or 5% concentrations following cryosurgery to cryosurgery with subsequent application of a vehicle. Efficacy of the combination therapy was assessed by complete clearance rates, lesion reduction (in some studies), and cosmetic appearance. All efficacy outcomes favored the use of the combined treatment over cryosurgery alone (Supplemental e-Table 7b). At 22 weeks post treatment, rates of complete clearance were 22.6% in participants treated with a combination of 5% imiquimod and cryosurgery and 9.4% in participants treated with a vehicle cream and cryosurgery (RR, 2.41; 95% CI, 0.68-8.48; P = .17). In participants treated with 3.75% imiquimod in combination with cryosurgery, the incidence of complete clearance at 26 weeks post treatment was 30.2% compared to 3.3% for participants treated with a vehicle cream and cryosurgery (RR, 9.12; 95% CI, 3.36-24.79; P < .0001). Moderate difference in harms to patients with the use of imiquimod combined with cryosurgery was seen as the participants in these studies who received combination therapy had increased rates of localized skin reactions and other adverse events.

Overall, the Work Group considered the benefits of the combined treatment of imiquimod and cryosurgery to probably outweigh the harms. Thus, the intervention is conditionally recommended over cryosurgery alone, based on this low quality evidence.

A multicenter, open-label study examined the efficacy and safety of the adjunctive use of topical
diclofenac sodium (DFS) after cryosurgery to maximize the complete clearance of AKs (Supplemental e-Table 7c). Patients were randomized to receive either cryosurgery followed by 90 days of topical treatment with 3% DFS, or cryosurgery alone. The rates of complete clearance in the study differed moderately in favor of combination therapy with cryosurgery and diclofenac over cryosurgery alone (45.9% vs 20.9% [RR, 2.19; 95% CI, 1.68–2.86; *P* < .0001], respectively). However, the rate of adverse events leading to discontinuation of treatment was significantly higher in the combination therapy group compared to the cryosurgery alone cohort (8.4% vs 1.2% [RR, 7.29; 95% CI, 2.60–20.43; *P* = .0002, respectively]). Furthermore, the Work Group considered the addition of a 90-day topical treatment to represent a burden likely to diminish treatment value for patients, given the modest increase in lesion reduction reported with the combined use of diclofenac and cryosurgery. Thus, the Work Group conditionally recommends against the use of 3% diclofenac in addition to cryosurgery, favoring cryosurgery alone based on this low quality evidence.

A randomized, comparative study examined the possible additive effect of using the daily application of 0.1% adapalene gel for 90 days beginning 10 days after cryosurgery for AK lesion reduction. There was no significant increase in lesion reduction in the patients receiving adapalene after cryosurgery, compared to those who receive a vehicle gel after cryosurgery (Supplemental e-Table 7d). The mean baseline number of AKs in the cryosurgery plus adapalene gel group was 7.54 ± 3.66, compared with 7.20 ± 3.60 for the cryosurgery plus placebo group. The mean number of lesions was reduced to 3.44 ± 2.71 (percent change from baseline −54.79 ± 3.88%) in the adapalene group and 3.68 ± 2.97 (percent change from baseline −48.60 ± 4.5%) in the placebo group (*P* = .62). Due to the lack of perceived benefit of an additional 90-day treatment, the Work Group conditionally recommends against the use of adapalene gel in addition to cryosurgery for the treatment of AK, based on this low quality evidence.

The effects of adding topical 5% imiquimod treatment as a twice-weekly therapy for 16 weeks beginning the second month following 2 cycles of ALA-blue light PDT was studied in a split-face fashion, with half of the face randomized to vehicle cream and the contralateral side to 5% imiquimod. Overall, there was a very small, but significant, increase in lesion reduction favoring the imiquimod treatment side (Supplemental e-Table 7e). At baseline, median lesion counts were 23.5 and 21.5 for the imiquimod and vehicle-treated sides, respectively. Median lesion reduction was 89.9% for the imiquimod-treated side and 74.5% for the vehicle-treated side at 12 months post treatment (*P* = .0023). However, there was no difference in rates of complete clearance between the treatment sides (83% for both sides). There were no differences in harms reported between the control and intervention sites. The Work Group conditionally recommends against the use of imiquimod topically after ALA-blue light PDT, based on this moderate quality data. The additional treatment with imiquimod was thought to add both expense and burden to the patient, which negates much of the perceived convenience of using PDT as a stand-alone treatment modality and which is not mitigated by the modest increase in lesion reduction.

**INSUFFICIENT EVIDENCE TO MAKE RECOMMENDATIONS**

The systematic review identified many studies of other interventions and comparisons of interventions for the management of AK that did not provide sufficient evidence for the Work Group to assess the balance of benefits and harms of treatment and to issue a recommendation. A list of interventions and comparisons of interventions identified, evaluated, and not considered to be viable candidates for recommendation development due to insufficient evidence is available in Supplemental e-Appendix 3.

**Follow-up**

Follow-up for patients with AK after initial treatment involves assessing treatment success, recurrence of treated lesions, and development of new AKs. Follow-up considerations are presented in Supplemental e-Appendix 5.

**GAPS IN RESEARCH**

**Immunocompromised patients**

One of the clinical questions raised by the Work Group at the start of guideline development was whether there are special considerations for the treatment of AK in immunocompromised individuals. These patients often have more advanced or complex presentations and are recognized to be at increased risk for the development of cutaneous malignancies, particularly SCC. A lack of evidence prevented development of recommendations for treatment in this patient population. The high level of evidence required from larger RCTs can be difficult to achieve for interventions when the patient population is constricted to a very specific subset, such as patients with chronic lymphocytic leukemia or with solid organ transplants. In this case, observational studies of high quality can be
used to assist in making therapeutic decisions backed by evidence but are beyond the scope of this guideline.

**Keratinocyte carcinoma prevention**

Although there is a strong theoretic rationale for the treatment of AK to prevent skin cancers, few of the studies included in this review report the incidence of skin cancer as an outcome measure or have sufficient follow-up to viably measure carcinoma development. Although the Work Group specified the incidence of cancer as an outcome of interest, the lack of evidence on keratinocyte carcinoma development may reflect the focus of this evidence review on the treatment of AK and not skin cancer prophylaxis.

A recently published analysis of pooled data from 2 randomized trials comparing the efficacy of treatment of facial AKs with 5% imiquimod and 3% DFS reported on the histologic progression of AKs to invasive SCC up to 36 months after treatment. Progression of AKs to invasive SCC, defined as the histologic finding of an invasive SCC in the treatment area after the start of treatment, was reported in 4 of 242 (1.7%) patients treated with imiquimod and in 7 of 237 (3.0%) patients treated with DFS. A large RCT of topical 5% 5-FU for chemoprevention of keratinocyte carcinoma demonstrated that a standard 2- to 4-week course of treatment of the face decreased 1-year SCC risk by 75% (95% CI, 35-91; \( P = .002 \)). Although this trial supports prophylactic use of 5-FU for cancer prevention, more long-term research is needed to validate our current understanding of skin cancer progression from AKs to keratinocyte carcinoma and the potential mitigating effects of treatment.

Additional gaps in research are presented in Supplemental e-Appendix 6.

**SUMMARY**

Analysis of the evidence from this systematic review based on 5 research questions resulted in 18 evidence-based recommendations and suggests there are several effective treatments available for AK. Strong recommendations were made for the use of UV protection, cryosurgery, topical imiquimod, and 5-FU. Conditional recommendations were made for the use of PDT and diclofenac for the treatment of AK, both individually and as part of combination therapy regimens. This analysis is based on the best available data at the time it was conducted. The results of future studies may necessitate revision of current recommendations.

Analysis limitations included the pragmatic decision to limit the literature review to English language, which may have excluded relevant data published in other languages. Due to the large scope of the review, the analysis included only randomized trials, which may have limited identification of relevant long-term follow-up data.

**Work group members disclosures**

Authors (listed alphabetically) with relevant conflicts of interest with respect to this guideline are noted with an asterisk (*).

Maryam M. Asgari, MD, MPH, serves as an investigator for Pfizer, Inc. receiving grants and/or research funding.

Daniel D. Bennett, MD, has no relationships to disclose.

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Esther E. Freeman, MD, PhD, has no relationships to disclose.

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Peggy A. Wu, MD, serves on the Board of Directors of the American Contact Dermatitis Society receiving no compensation; as a panel review committee member for the National Eczema Association receiving honoraria; as an independent contractor for UpToDate, Inc receiving honoraria.

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APPENDIX 1

Detailed methods

Expert work group composition and disclosures of interest. The Co-Chairs of the Work Group (T.S. and D.E.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD’s Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the Co-Chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on recommendations in which they had relevant DOIs. Work Group members completed a disclosure of interests form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the Co-Chairs, 8 members, an additional member serving as a methodologist, and a representative from a patient advocacy organization.

Formulation of questions and rating the importance of outcomes. The expert Work Group identified 5 clinical questions on the management of actinic keratoses using the Population, Intervention, Comparator, Outcome (PICO) format (Table V). After selecting the questions that would be addressed in the guideline, the Work Group identified outcomes considered important for making clinical decisions regarding the treatment of AKs (Table VI). The Work Group ranked the importance of each primary outcome for decision-making via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).141 Results of voting were used to categorize outcomes as “critical,” “important,” or “not important.”

Literature searches. AAD partnered with Doctor Evidence, LLC (Doctor Evidence: Library Management System. Santa Monica, CA: Doctor Evidence, LLC) to conduct components of the systematic review process, including literature searches and study selection. Doctor Evidence, LLC performed a systematic search of the literature for all PICO questions using MEDLINE (via PubMed), EMBASE, and CENTRAL (via OVID). Databases were searched from inception through January 10, 2019. A combination of the National Library of Medicine’s medical subject headings and other keywords specific to each PICO question was used to identify studies. MEDLINE (via PubMed) search strategies are available (Supplemental e-Appendix 1). Searches were limited to English language results. Studies were not limited by study design or publication date; however, the inclusion criteria limited study design to randomized controlled trials. The literature search identified a total of 6240 eligible studies. After 2 rounds of study screening, 41 were selected for the final evidence review.

Study selection and data extraction. Studies retrieved by the literature searches were reviewed for relevance over 2 rounds of study selection. During the first round of study selection, title and abstract screening was performed against predefined inclusion and exclusion criteria by Doctor Evidence, LLC. Title and abstract screening was performed via a dual review with subsequent quality control by an independent reviewer. The full text of studies appearing to meet inclusion criteria during title and abstract screening were retrieved and then underwent a second round of study selection, during which a final inclusion decision was made. Full text screening inclusion decisions were made independently and in parallel by 2 Work Group members. Disagreements were resolved through discussion by the original pair of reviewers to reach a consensus.

Structured data tables were used to extract relevant data from all included studies. Data extraction was initially performed by an independent methodologist (L.F.G) with subsequent quality control performed by an additional independent reviewer. Discrepancies were resolved through discussion by the original data extractor and the independent reviewer.

Risk of bias assessment and evidence synthesis. The risk of bias was assessed in all included studies using the Cochrane Collaboration’s tool for assessing the risk of bias in randomized trials.142 Following risk of bias assessment, the Cochrane Collaboration Review Manager, version 5.3 was used to conduct meta-analyses when data were homogeneous and poolable. Individual estimates were pooled using a random-effects model and the method of DerSimonian and Laird.143,144 For dichotomous and continuous outcomes risk ratios and mean differences with accompanying 95% CIs were reported, respectively. Statistical heterogeneity was assessed using the Higgins I² value and the χ² test.
A Higgins’ $I^2$ value $\geq 50\%$ and $P$ values $< .05$ were considered to represent significant heterogeneity.

**Assessing the overall quality of the body of evidence.** The GRADE approach was used to assess the overall certainty of the evidence for each critical or important outcome. The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall quality of the body of evidence for each outcome into 1 of 4 categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (Table VII).

**Formulating and grading recommendations.** The Work Group drafted recommendations using the evidence profiles and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, and feasibility. In accordance with the GRADE approach, recommendations were either “strong” or “conditional.” The implications of each strength of recommendation are summarized in Table VIII.

Recommendations were also graded according to the GRADE approach. In situations in which the supporting evidence for a recommendation was indirect only, but the certainty surrounding an intervention’s impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed. Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

**Manuscript review and currency statement.** This guideline has been developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (November 2019), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors. This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.
## Table V. Clinical questions (CQ)

<table>
<thead>
<tr>
<th>Question element</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CQ1: Should topically applied agents be used for the treatment of AKs?</strong></td>
<td>Population: Adults (≥18 years of age) with a clinical or histopathologic diagnosis of AK</td>
<td>Individuals with actinic cheilitis</td>
</tr>
<tr>
<td>Intervention: Any topical therapy available, approved, and used in clinical practice in the US</td>
<td>Treatments not available, approved, or regularly used in clinical practice in the US</td>
<td></td>
</tr>
<tr>
<td>Comparator: Placebo, observation, other monotherapy, or combined therapy of other interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CQ2: Should surgical and/or chemical therapies be used for the treatment of AKs?</strong></td>
<td>Population: Adults (≥18 years of age) with a clinical or histopathologic diagnosis of AK</td>
<td>Individuals with actinic cheilitis</td>
</tr>
<tr>
<td>Intervention: Surgical approaches, cryosurgery, curettage, peels, dermabrasion, electrosurgery</td>
<td>Treatments not available, approved, or regularly used in clinical practice in the US</td>
<td></td>
</tr>
<tr>
<td>Comparator: Placebo, observation, other monotherapy, or combined therapy of other interventions</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CQ3: Should energy devices and other miscellaneous therapies be used for the treatment of AKs?</strong></td>
<td>Population: Adults (≥18 years of age) with a clinical or histopathologic diagnosis of AK</td>
<td>Individuals with actinic cheilitis</td>
</tr>
<tr>
<td>Intervention: Ablative lasers, photodynamic therapy, oral therapy, sun protection</td>
<td></td>
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</tr>
<tr>
<td>Comparator: Placebo, observation, other monotherapy, or combined therapy of other interventions</td>
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</tr>
<tr>
<td><strong>CQ4: Should combination therapy be used for the treatment of AKs?</strong></td>
<td>Population: Adults (≥18 years of age) with a clinical or histopathologic diagnosis of AK</td>
<td>Individuals with actinic cheilitis</td>
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<tr>
<td>Intervention: Therapy that includes the combined use of more than 1 treatment</td>
<td>Treatments not available, approved, or regularly used in clinical practice in the US</td>
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<tr>
<td>Comparator: Placebo, observation, other monotherapy, or combined therapy of other interventions</td>
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</tr>
<tr>
<td><strong>CQ5: Should special consideration be taken when treating AKs in immunocompromised individuals?</strong></td>
<td>Population: Immunosuppressed patients or organ transplant recipients with a clinical or histopathologic diagnosis of AK</td>
<td>Individuals with actinic cheilitis</td>
</tr>
<tr>
<td>Intervention: Any therapy available and approved for use in clinical practice in the US</td>
<td>Treatments not available, approved, or regularly used in clinical practice in the US</td>
<td></td>
</tr>
<tr>
<td>Comparator: Placebo, observation, other monotherapy, or combined therapy of other interventions</td>
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</tr>
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</table>

AK, Actinic keratosis; US, United States.
Table VI. Primary outcomes

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Importance ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean reduction in AK counts from baseline to assessment</td>
<td>Critical</td>
</tr>
<tr>
<td>Participant complete clearance (participants with a complete clearance of all AKs within a predefined field)</td>
<td>Critical</td>
</tr>
<tr>
<td>Participant partial clearance (participants with at least a 75% reduction in the AKs within a predefined field)</td>
<td>Critical</td>
</tr>
<tr>
<td>Investigator global improvement index (participants rated as “completely improved” by the investigator)</td>
<td>Critical</td>
</tr>
<tr>
<td>Participants global improvement index (participants self-assessed as “completely improved”)</td>
<td>Critical</td>
</tr>
<tr>
<td>Withdrawals due to adverse events</td>
<td>Critical</td>
</tr>
<tr>
<td>Adverse events</td>
<td>Important</td>
</tr>
</tbody>
</table>

AK, Actinic keratosis.
Table VII. Certainty of evidence ratings

<table>
<thead>
<tr>
<th>Certainty of the evidence</th>
<th>Confidence in the estimate of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
</tbody>
</table>
Table VIII. Strength of recommendation implications

<table>
<thead>
<tr>
<th>Strength</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh the benefits</td>
</tr>
<tr>
<td>Conditional</td>
<td>Benefits finely balanced with risks and burden</td>
</tr>
</tbody>
</table>