Aggiornamenti sugli algoritmi terapeutici per la cheratosi attinica

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Roma
Eradicate as many clinical and subclinical AK lesions as possible

Achieve clinical remission that is as prolonged as possible

Provide a good cosmetic result

Prevent the progression to invasive SCC
Treatment algorithm for actinic keratosis

**Diagnosis of AK**

- High risk actinic keratosis (e.g. immunosuppressed and/or high risk location levels)
- Actinic keratosis

**Lesion Evaluation**

- Multiple lesions (high number concentrated in a small area) or history of multiple lesions
- Solitary lesions

**Treatment Options**

- Refer to a dermatologist for a specific management
- Lesion and field directed treatment recommended
- Lesion directed treatment

- Diclofenac 3% gel
- Imiquimod
- PDT
- 5-FU
- All + Sun protection
- Treatment of lesion and surrounding skin/field (Diclofenac 3% gel, Imiquimod, PDT, 5-FU)
- All + Sun protection

- Chemical peels
- Retinoids
- All + Sun protection

- Cryotherapy
- Laser therapy
- Surgery*
- All + Sun protection

*Histological investigation is recommended before surgery

**Stockfleth et al EJD 2008**
in these patients. AK treatment should be considered before organ transplantation. A regular clinical follow-up is carried out by the dermatologist for early detection and treatment of these lesions. In addition, patient education on skin self-examination is fundamental and allows delaying the development of potential cancerous lesions in transplant patients.

### Monitoring and secondary prevention

Patients with AK should be monitored regularly because of the chronic nature of lesions and an invasive SCC should be detected as early as possible. In patients at risk, the monitoring rate proposed is at least a yearly consultation. During these consultations, the patient should be educated on the need for reconsulting earlier if any lesion changes rapidly or in case of recurrence after treatment. Organ transplant patients must be managed in a particular way, especially in terms of personalized monitoring. Sun protective clothing and behaviour, and the use of sun-screen products (chemical or mineral filters), should be recommended to patients to minimize the worsening of photo-induced skin damage and to prevent skin cancer. It has been demonstrated that sunscreen is an effective AK prevention method. Applying sunscreen (greater than SPF-15 applied every 2–3 h) reduces the risk of AK lesions by up to 24% over time, even compared with beta-carotene and topical tretinoin cream 0.05%.

### Conclusions

The objective of this expert panel report was to provide a pragmatic solutions for dermatologists in terms of diagnosis, monitoring and a treatment algorithm that they could use in their daily practice, based on data from the literature and former guidelines.

### Acknowledgements

We would like to thank Dr Maxime Battistella, Service de Pathologie de l’Hôpital Saint Louis in Paris, for his help in the writing of this article.

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**Table: Treatment Algorithm for AK Management, Depending on Lesion Number and Appearance**

<table>
<thead>
<tr>
<th>Lesion Number</th>
<th>Evaluation of Lesions</th>
<th>1st line</th>
<th>2nd line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-hyperkeratotic AK</td>
<td>● Cryotherapy</td>
<td>● Surgery if recurrence / resistance</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratotic AK</td>
<td>● Cryotherapy</td>
<td>● Surgery if recurrence / resistance</td>
<td></td>
</tr>
<tr>
<td>Suspicious AK</td>
<td>● Biopsy + exeresis</td>
<td>● Surgery if recurrence / resistance</td>
<td></td>
</tr>
<tr>
<td>Non-hyperkeratotic AK</td>
<td>● Biopsy *</td>
<td>● Surgery if recurrence / resistance</td>
<td></td>
</tr>
<tr>
<td>Hyperkeratotic AK</td>
<td>● Resurfacing -manual -salicylic acid/urea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**topical treatments**
- 5% 5-fluorouracil
- 3% diclofenac sodium
- 5% imiquimod
- 150 μg/g and 500 μg/g ingenol mebutate

**physical treatments**
- laser
- photodynamic therapy

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*Confirmation of diagnosis of actinic keratosis (AK): Refer to treatment algorithm
AK, actinic keratosis

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JEADV 2014, 28, 1141–1149

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should be noted that, after removal of hyperkeratosis with the application of salicylic acid or thiourea, all topical therapies can be effectively used on such lesions.

Among field-directed therapies, only IngMeb, IMQ 5% 4 week, DF/HA and MAL-PDT are available in Italy. Both placebo-controlled and head-to-head RCTs demonstrated the efficacy of field-directed treatments in eliminating visible lesions, subclinical lesions, patches of fast-growing atypical keratinocytes within CF and decreasing recurrence rates. Achievement of such intermediate endpoints is thought to translate in lower iSCC rates. However, no long-term study has definitely proven such well-found assumption.

The evidence base for both lesion-directed and field-directed therapies is summarized in Appendix S1. Overall, there is a wide variation in clearance rates across studies of the same treatment modality, which complicates the interpretation of each RCT in the light of the pre-existing evidence. Such variation might be explained by heterogeneity in study design, case mix, follow-up period, outcome definition and ascertainment methods. Ideally, a parallel group randomized controlled trial should assess the comparative efficacy of all options available. A phase IV RCT comparing the clinical and pharmaco-economic outcomes of IngMeb, IMQ 5%, MAL-PDT and 5-FU [RCT ID: NCT02281682] along with several head-to-head RCTs are ongoing.

*Field-directed therapies may also be considered for a large single lesion when its borders cannot be delimited accurately or in patients who failed previous treatments with cryotherapy (i.e. recurrence in the same area within 12 months). **Single or multiple cycles depending on the extent of the affected area

Peris K et al. JEADV 2015
# S3 Guidelines recommendations

<table>
<thead>
<tr>
<th>Decreasing strength of recommendation</th>
<th>Single AK lesions (≤5)</th>
<th>Multiple AK lesions ≥6</th>
<th>Field cancerization</th>
<th>Immuno-compromised patients with AK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong</strong></td>
<td>Cryotherapy</td>
<td>3.75% imiquimod MAL-PDT/ALA-PDT 0.5% 5-FU Ingenol mebutate 0.015%-0.05%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weak</strong></td>
<td>Curettage 0.5% 5-FU/5% 5-FU 0.5% 5-FU + 10% SA 3.75% imiquimod 5% imiquimod Ingenol mebutate MAL-PDT/ALA-PDT</td>
<td>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</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NO</strong></td>
<td>3% diclofenac 2.5% imiquimod CO2-laser Er:YAG-laser</td>
<td>Curettage</td>
<td>3% diclofenac 0.5% 5-FU 0.5% 5-FU + 10% SA 2.5%/3.75% imiquimod Ingenol mebutate</td>
<td></td>
</tr>
</tbody>
</table>

- **ILDS and EDF JEADV 2015**

- Sunprotection in all patients subgroups
AK definition/diagnosis and factors influencing AK treatment decision making

A set of 3 clinical cases whereby participants were required to assess the nature of AK, list their preferred management options, and express their view on the appropriateness of dl-PDT use
A list of treatment options for the management of AK was developed from the outputs of the Delphi panel and the systematic literature searches. The expert panel consisted of 16 clinical experts with extensive experience on AK and their ability to assess the appropriateness of dl-PDT use. The one-off questionnaire and Delphi panel were communicated and collected via email and included 8 and 33 participants, respectively, with a median of 75 AK patients seen on a weekly basis. The median number of clinical trials they had participated in as an investigator over the previous 5 years was 12,18-21.

**Exclusion criteria**
- Duplicate, not in the language of interest (English), abstract that is reported elsewhere
- Locations of interest: European Union, Latin America, Australia, Canada
- Dermatology organisations, relevant conference abstract/posters (from 2012)

**Hand searches**
- Study Type: Clinical guidelines from recognised large organisations, consensus statements
- Comparator: No restriction
- Outcome of interest: Recommendations for the management of AK
- Study type of interest: Treatment guideline or recommendation
- Conference abstracts of interest: published 2012-2015

**Searches identified 612 citations for screening via database**
- Systematic Literature Review Methodology and Search Results.
- MEDLINE
- EMBASE

**Critical assessment of the extracted guidelines was performed using the AGREE II guideline evaluation tool. Three**
- Some guidelines also formed using the AGREE II guideline evaluation tool. Three
- Certain guidelines imposed an overly theoretical approach to treatment, such as prolonged treatment period that would likely prove difficult for some patients.
- Reporting of strength of evidence

**Results associated with methodological concerns for the remaining guidelines (see Appendix 2). However, reporting of strength of evidence**
- Some guidelines also formed using the AGREE II guideline evaluation tool. Three
- Certain guidelines imposed an overly theoretical approach to treatment, such as prolonged treatment period that would likely prove difficult for some patients.
- Reporting of strength of evidence

**Table 2**

<table>
<thead>
<tr>
<th>Area of Field</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISOLATED AK I/II</td>
<td>Cryotherapy, C-PDT, Imiquimod, 5-FU, Ingenol Mebutate</td>
</tr>
<tr>
<td>MULTIPLE AK I-III IN AN AREA OF FIELD CANCERIZATION</td>
<td>C/dI-PDT, 5-FU, Imiquimod, Ingenol Mebutate</td>
</tr>
<tr>
<td>MULTIPLE AK I-III AND FIELD CANCERIZATION</td>
<td>C/dI-PDT, 5-FU, Imiquimod</td>
</tr>
</tbody>
</table>

**Photograph representing clinical case 1. Source:**
- Ingenol

**Photograph representing clinical case 2. Source:**
- Cryotherapy, Imiquimod

**Photograph representing clinical case 3. Source:**
- C/dI-PDT, 5-FU, Imiquimod
Table 8. Findings for the Assessment, Treatment, and Use of dl-PDT for Clinical Cases 1, 2, and 3.

<table>
<thead>
<tr>
<th>Clinical Case</th>
<th>Assessment</th>
<th>Treatment</th>
<th>dl-PDT Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—Round 3</td>
<td>Isolated AK grades I/II with uncertainty regarding field cancerisation. (CL: 10)</td>
<td>Although there is a risk of hypopigmentation, cryotherapy is among the first treatment options. Then (order varies) c-PDT, imiquimod or 5-FU, and ingenol mebutate. (CL: 8)</td>
<td>dl-PDT (most often to the whole face) is more appropriate when there are multiple AKs and/or suspecting a cancerisation field. In the case of single lesions, more practical alternatives are preferable. Reimbursement status may affect the use of dl-PDT. (CL: 9)</td>
</tr>
<tr>
<td>2—Round 3</td>
<td>Multiple AK grades I, II, and III in an area of field cancerisation. (CL: 10)</td>
<td>Biopsy is considered for thick lesions. Prior to treatment, field preparation using curettage is required. First option for treatment is c-PDT, then (order varies) dl-PDT or 5-FU. Last, imiquimod and ingenol mebutate may be used. (CL: 9)</td>
<td>dl-PDT is appropriate for the thinner lesions. Thicker lesions must be treated separately and prior to dl-PDT. (CL: 10)</td>
</tr>
<tr>
<td>3—Round 3</td>
<td>Multiple AK grade I/II and field cancerisation. (CL: 10)</td>
<td>Field treatment is required, with preferably dl-PDT but also c-PDT, imiquimod, and 5-FU. (CL: 9)</td>
<td>Yes. This choice may depend on dl-PDT reimbursement status and sun exposure (season/location). (CL: 10)</td>
</tr>
</tbody>
</table>

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

a Exact questions asked: ‘The following three questions are clinical cases. On the basis of the following pictures, please assess the clinical features of AK and the most appropriate treatment to provide. Please assume that patients are not immunocompromised. (1) Clinical assessment of clinical case 1/2/3. (2) What are the most appropriate treatments for clinical case 1/2/3? (3) Is daylight PDT relevant for clinical case 1/2/3?’
• Published data from RCT are the “gold standard” evidence to support the treatment recommendations
<table>
<thead>
<tr>
<th>THERAPY</th>
<th>AK TYPE</th>
<th>Tx AREA</th>
<th>TREATMENT REGIMEN</th>
<th>DURATION</th>
<th>LESION CLEARANCE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 5% 5-FU</td>
<td></td>
<td>25 cm²</td>
<td>Twice daily</td>
<td>2-4 weeks Up to 12 wks</td>
<td>75-88</td>
</tr>
<tr>
<td>- 0.5% 5-FU + 10% salycilic acid</td>
<td></td>
<td></td>
<td>Once daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imiquimod 5% cream</td>
<td>I-II</td>
<td>25 cm²</td>
<td>3 times a week for 4 wks 4 wks off and 4 wks on, if needed</td>
<td>4 weeks</td>
<td>75.7</td>
</tr>
<tr>
<td>Imiquimod 3.75% cream</td>
<td>I-II</td>
<td>100-200 cm²</td>
<td>Daily 2 weeks on, 2 weeks off, 2 weeks on</td>
<td>2 + 2 weeks</td>
<td>92.2</td>
</tr>
<tr>
<td>Ingenol mebutate 150-500 mcg/g gel</td>
<td>I-II</td>
<td>25 cm²</td>
<td><strong>Face/scalp:</strong> 0.015% once daily for 3 consecutive days <strong>Trunk/extremities:</strong> 0.05% once daily for 2 consecutive days</td>
<td>2-3 days</td>
<td>75-83</td>
</tr>
<tr>
<td>Diclofenac 3% gel</td>
<td>ns</td>
<td></td>
<td>Twice daily</td>
<td>60-90 days</td>
<td>54-63</td>
</tr>
<tr>
<td>c/dIPDT</td>
<td></td>
<td>100 cm²</td>
<td>Prepare skin. Apply cream 3 hours under occlusion prior to illumination</td>
<td>1 day</td>
<td>82-91</td>
</tr>
</tbody>
</table>

Peris et al. 2015, 2016; Pellacani 2015, Fargnoli 2015, Dirschka 2016
Factors that drive treatment choice in real life clinical practice

Lesion characteristics

- **Number**
- **Thickness**
- **Distribution**
Factors that drive treatment choice

Patient variables

• Age (comorbidities)
• Ability to perform home-based treatment
• Patient’s immune status
• Adherence to the Tx regimen
• History of previous treatment

• Availability of drugs/procedure
• Dermatologist experience
Real-world approach to actinic keratosis management: practical treatment algorithm for office-based dermatology

Thomas Dirschka, Girish Gupta, Giuseppe Micali, Eggert Stockfleth, Nicole Basset-Séguin, Véronique Del Marmol, Reinhard Dummer, Gregor B. E. Jemec, Josep Malvehy, Ketty Peris, Susana Puig, Alexander J. Stratigos, Iris Zalaudek and Giovanni Pellacani

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ABSTRACT
Actinic keratosis (AK) is a chronic skin disease in which multiple clinical and subclinical lesions co-exist across large areas of sun-exposed skin, resulting in field cancerisation. Lesions require treatment because of their potential to transform into invasive squamous cell carcinoma. This article aims to provide office-based dermatologists and general practitioners with simple guidance on AK treatment in daily clinical practice to supplement existing evidence-based guidelines. Novel aspects of the proposed treatment algorithm include differentiating patients according to whether they have isolated scattered lesions, lesions clustered in small areas or large affected fields without reference to specific absolute numbers of lesions. Recognising that complete lesion clearance is rarely achieved in real-life practice and that AK is a chronic disease, the suggested treatment goals are to reduce the number of lesions, to achieve long-term disease control and to prevent disease progression to invasive squamous cell carcinoma. In the clinical setting, physicians should select AK treatments based on local availability, and the presentation and needs of their patients. The proposed AK treatment algorithm is easy-to-use and has high practical relevance for real-life, office-based dermatology.
AK CLASSIFICATION

**ISOLATED LESION**
- isolated individual lesions scattered on separate body areas

**MULTIPLE LESIONS CLUSTERED INTO A SMALL FIELD**

**MULTIPLE LESIONS ACROSS A LARGE FIELD (e.g. ENTIRE FACE OR SCALP)**
- 5 palpable or visible AK lesions
- those with multiple lesions clustered in a small field
- those with multiple lesions across a large field (entire face or scalp)

Clinical spectrum of AK

The authors propose that AK patients should be classified as:

1. Those with isolated individual lesions scattered on separate body areas;
2. Those with multiple AK lesions clustered into a single small field; and
3. Those with multiple lesions across a large field such as the entire face or scalp.

The latest ILDS/EDF AK guidelines classify patients according to the number of AK lesions per period has been taken. Therapies for large-affected fields are started after the initial cycle has been completed and a rest period has been taken. Cluster-directed therapies may also be used to distinguish those most likely to progress to invasive disease.

Therapies for large-affected fields are at the expense of an increased number of physician visits across a large field such as the entire face or scalp. Whilst the number of metastatic disease so that they can be monitored more closely.

Patients who are at high risk of progression to invasive SCC or malignancy.

Classification of AK lesions: (A) isolated lesion; (B) multiple lesions clustered in a small field; (C) multiple lesions across a large field (entire scalp).

- 5 distinguishable AK lesions, and those with field cancerisation areas of chronic actinic sun damage and hyperkeratosis.

A practical algorithm for the management of AK patients in real-life clinical practice is shown in Table 1.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated lesion</td>
<td>Lesions scattered on separate body areas</td>
</tr>
<tr>
<td>Multiple lesions clustered into a small field</td>
<td>Lesions clustered in a small field</td>
</tr>
<tr>
<td>Multiple lesions across a large field</td>
<td>Lesions across a large field (entire face or scalp)</td>
</tr>
</tbody>
</table>

Treatment recommendations are provided for patients with isolated scattered lesions, those with small clusters of lesions and rapid increase in lesions, immunosuppression or other factors that can influence the risk of developing an invasive SCC. The authors consider the ILDS/EDF patient classification to have limited supporting evidence for the numerical thresholds of characteristics of the disease process, in particular field cancerisation.

Treatment. Curettage is preferred because it allows histological confirmation of the diagnosis. Furthermore, the panel recommends taking biopsies and performing histopathology on residual lesions after topical treatment to explore the possibility of malignancy.

Table 1: Criteria suggestive of metastatic disease

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid increase in lesions</td>
<td>Increases in the number of lesions</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Immunosuppressed state</td>
</tr>
<tr>
<td>Other factors</td>
<td>Factors that can influence the risk of developing invasive SCC</td>
</tr>
</tbody>
</table>

**Practical Algorithm for AK Management**

1. **Patient Assessment**
   - History: Previous treatments, family history of skin cancer, immuno-suppression.
   - Physical examination: Skin examination, palpation of lymph nodes.

2. **Histological confirmation**
   - Biopsy: Indications for biopsy include rapid increase in lesions, immunosuppression, or other factors that can influence the risk of developing invasive SCC.

3. **Treatment Options**
   - **Isolated lesions**: Topical treatments (e.g., 5-fluorouracil, imiquimod).
   - **Multiple lesions clustered in a small field**:
     - Topical treatments: As above.
     - Cluster-directed therapies: Lectrin-directed therapies.
   - **Multiple lesions across a large field**: Systemic treatments (e.g., oral retinoids, photodynamic therapy).

4. **Follow-up**
   - Regular skin examinations to monitor for new lesions or progression.
   - Discharge criteria: No new lesions, stable disease.

**Key Points**

- **Classification of AK lesions** is useful to define patient eligibility criteria for RCTs.
- Field cancerisation also has implications for treatment and prognosis.
- **A practical algorithm** for the management of AK patients in real-life clinical practice is provided.

**References**

- Pellacani et al. (2023)
Lesion-directed therapies for *single or scattered lesions*

- Cryotherapy
- Topical active drugs
- Laser (CO$_2$; Er:Yag)
- Curettage

*Dirschka T et al JDT 2016*
Clustered-directed therapies (areas ≤25 cm²)

- Imiquimod 5%
- 0.5% 5-FU / 10% salicylic acid
- Ingenol Mebutate

All large field-directed therapies can be used to treat clusters.
Large field-directed therapies for multiple lesions

- IMQ 3.75%
- 5-FU
- Diclofenac gel
- PDT

Clustered-directed therapies may be used to treat large fields in successive treatment cycles.
The goals of AK treatment are to eradicate as many clinical and subclinical AK lesions as possible (i.e. to reduce the extent of field cancerisation), to achieve a time to relapse or disease-free interval following treatment.

In real-life clinical practice, treatment success should usually be evaluated using the absolute or percentage reduction in AK lesions, rather than by determining whether or not the patient has had new lesions. Treatment success is also influenced by the number of lesions the patient has on presentation and the individual clinical situation.

A 95% reduction in lesions has been achieved. Treatment success is based on the endpoint of complete lesion clearance, even though many AK lesions are not usually available in dermatological offices.

TREATMENT SUCCESS EVALUATION AFTER 3 TO 6 MONTHS

Lesion-directed therapies

Cluster-directed therapies

Large field-directed therapies

Dirschka T et al. JDT 2016
Lesion clearance rate: 81.3% (vs 78% in RCT)

- Scalp lesions had a higher clearance rate compared to RCT (80% vs 53%)
• No differences in clearance rate for patients who were *previously treated* compared to naïve patients
• No differences according to patients’ age, sex and baseline number of AK lesions
• No difference of efficacy *across treatment cycles*
<table>
<thead>
<tr>
<th>IMIQUIMOD 5%</th>
<th>IMIQUIMOD 3.75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can be used to treat <em>small clusters of lesions</em> in a 25 cm² area</td>
<td></td>
</tr>
<tr>
<td>• Self-applied 3 times/week for 4 wks; 4 wks free interval, II 4wks course</td>
<td></td>
</tr>
<tr>
<td>• Can detect and treat both clinical and subclinical lesions</td>
<td></td>
</tr>
<tr>
<td>• Clearance rate: 75%</td>
<td></td>
</tr>
<tr>
<td>• Used to treat large affected fields (i.e. full face or balding scalp) in sequential treatment courses (high cost)</td>
<td></td>
</tr>
<tr>
<td>• Can be used to treat <em>large affected fields</em> (i.e. full face or balding scalp) in one treatment course</td>
<td></td>
</tr>
<tr>
<td>• Self-applied once daily for 2 wks treatment cycles separated by a 2-wks free interval</td>
<td></td>
</tr>
<tr>
<td>• Can detect and treat both clinical and subclinical lesions</td>
<td></td>
</tr>
<tr>
<td>• 81.8% median percentage reduction in AK lesions from baseline</td>
<td></td>
</tr>
<tr>
<td>• Sustained clinical response over long-term</td>
<td></td>
</tr>
</tbody>
</table>

Diclofenac 3% in 2.5% hyaluronic acid

- NSAD which inhibits cyclooxygenase 2
- Treat *clustered lesions* and *field cancerisation*
- Overall lesion clearance rates reported in RCTs: 54–63%
- Advantage: good tolerability with only mild irritant side effects (pruritus, erythema and dry skin; rare: contact dermatitis)
- Treatment duration is long (60-90days): difficult for many patients to fully comply

Wolf JE IJD 2001; Rivers JK BJD 2002; Gebauer K AJD 2003, Nelson CG TCRM 011
Hyperkeratotic AK

Before any specific treatment

- Urea 10-30% cream
- Salicylic acid 10%
- Gentle curettage
TREATMENT OF ACTINIC CHEILITIS

- Cryosurgery
- 5% 5-FU
- MAL-PDT followed by IMQ
- Ingenol Mebutate
- Surgical vermilionectomy

NO RCT!

Sotiriou E BJD 2011; Tzika E Dermatology 2016; Florez A JDT 2016; Chaves YN Photodermatol Photoimmunol Photomed 2016;
AK treatment in OTR

- Cryotherapy
- Curettage and electrodesiccation
- PDT
- Imiquimod*
- Ingenol mebutate**
- Diclofenac 3%
- Systemic retinoids

*off label
**no studies
Combined or sequential treatments

- Laser
- 5-Fluorouracil
- Imiquimod
- Photodynamic therapy
- Diclofenac 3%
- Cryotherapy

SURGERY
Combined or sequential treatments

- **Field-treatment** followed by cryo to target individual, resistant lesions

- **Lesion-directed** treatment followed by field-directed therapy, used to treat the actinic damage in the surrounding area
  - Cryosurgery followed by imiquimod 3.75%
  - Cryosurgery followed by 5-fluorouracil
  - PDT followed by imiquimod 5%
  - 5-FU followed by ALA-PDT
  - Diclofenac 3% followed by PDT

CONCLUSIONS

• Deliver simple yet complete information about the modality of self-administration (apply to the target area or the whole area, e.g. full scalp or face) and the expected course of therapy

• Routine follow-up evaluation (every 3-6 months) to examine skin carefully and identify new, early AK lesions as well as other skin cancers

• Sunprotection! Instruct the patient to avoid excessive sun-exposure and to use sunscreen daily