



# European Dermatology Forum

## Guideline on Actinic Keratoses

Developed by the Guideline Subcommittee “Actinic Keratoses” of the  
**European Dermatology Forum**

### *Subcommittee Members:*

Prof. Dr. Eggert Stockfleth, Berlin (Germany)  
Dr. Dorothea Terhorst, Berlin (Germany)  
Prof. Dr. Lasse Braathen, Bern (Switzerland)  
Prof. Dr. Rino Cerio, London (UK)  
Prof. Dr. Carlos Ferrándiz, Barcelona (Spain)  
Prof. Dr. Alberto Giannetti, Modena (Italy)

Prof. Dr. Lajos Kemény, Szeged (Hungary)  
Prof. Dr. Bernt Lindelöf, Stockholm (Sweden)  
Prof. Dr. Martino Neumann, Rotterdam (Netherlands)  
Prof. Dr. Wolfram Sterry, Berlin (Germany)  
Prof. Dr. Helmut Kerl, Graz (Austria)

### *Members of EDF Guideline Committee:*

Prof. Dr. Werner Aberer, Graz (Austria)  
Prof. Dr. Martine Bagot, Créteil (France)  
Prof. Dr. Ulrike Blume-Peytavi, Berlin (Germany)  
Prof. Dr. Lasse Braathen, Bern (Switzerland)  
Prof. Dr. Sergio Chimenti, Rome (Italy)  
Prof. Dr. José Luis Diaz-Perez, Bilbao (Spain)  
Prof. Dr. Claudio Feliciani, Rome (Italy)  
Prof. Dr. Claus Garbe, Tübingen (Germany)  
Prof. Dr. Harald Gollnick, Magdeburg (Germany)  
Prof. Dr. Gerd Gross, Rostock (Germany)  
Prof. Dr. Vladimir Hegyi, Bratislava (Slovakia)  
Prof. Dr. Michael Hertl, Marburg (Germany)  
Prof. Dr. Lajos Kemény, Szeged (Hungary)  
Prof. Dr. Robert Knobler, Wien (Austria)

Prof. Dr. Hans-Christian Korting, Munich (Germany)  
Prof. Dr. Gilian Murphy, Dublin (Ireland)  
Prof. Dr. Martino Neumann, Rotterdam (Netherlands)  
Prof. Dr. Tony Ormerod, Aberdeen (UK)  
Prof. Dr. Mauro Picardo, Rome (Italy)  
Prof. Dr. Johannes Ring, Munich (Germany)  
Prof. Dr. Annamari Ranki, Helsinki (Finland)  
Prof. Dr. Berthold Rzany, Berlin (Germany)  
Prof. Dr. Sonja Ständer, Münster (Germany)  
Prof. Dr. Eggert Stockfleth, Berlin (Germany)  
Prof. Dr. Alain Taieb, Bordeaux (France)  
Prof. Dr. Nikolai Tsankov, Sofia (Bulgaria)  
Prof. Dr. Elke Weisshaar, Heidelberg (Germany)  
Prof. Dr. Fenella Wojnarowska, Oxford (UK)

### *Chairman of EDF Guideline Committee:*

Prof. Dr. Wolfram Sterry, Berlin (Germany)

Expiry date: 11/2014

---

*EDF Guidelines Secretariat to Prof. Sterry:*

Bettina Schulze, Klinik für Dermatologie, Venerologie und Allergologie, Campus Charité Mitte,  
Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany  
phone: ++49 30 450 518 062, fax: ++49 30 450 518 911, e-mail: bettina.schulze@charite.de

## Conflicts of interests

### Guidelines for the management of actinic keratoses (Eggert Stockfleth et al.)

The Work Under Consideration for Publication					
		<b>Martino Neumann</b>	<b>Dorothea Terhorst</b>	<b>Bernt Lindelöf</b>	<b>Alberto Giannetti</b>
1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	No	No	No
3	Support for travel to meetings for the study or other purposes	Medi	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	No
2	Consultancy	No	No	No	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	No	No	No	No
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No
10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	No

13	Other (err on the side of full disclosure)	No	No	No	No
----	--	----	----	----	----

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

## Conflicts of interests

### Guidelines for the management of actinic keratoses (Eggert Stockfleth et al.)

The Work Under Consideration for Publication					
		<b>Carlos Ferrándiz</b>	<b>Helmut Kerl</b>	<b>Lasse Braathen</b>	<b>Lajos Kemeny</b>
1	Grant	No	No	No	No
2	Consulting fee or honorarium	No	Meda/Almirall	No	No
3	Support for travel to meetings for the study or other purposes	No	No	No	No
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	No	No
5	Payment for writing or reviewing the manuscript	No	No	No	No
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	No	No
7	Other	No	No	No	No

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	No	Abbott, Pfizer, Janssen-Cilag, MSD, LEO
2	Consultancy	Almirall	No	Galderma	No
3	Employment	No	No	No	No
4	Expert testimony	No	No	No	No
5	Grants/grants pending	No	No	No	No
6	Payment for lectures including service on speakers bureaus	Almirall	No	Galderma	Abbott, Pfizer, Janssen-Cilag, MSD, Galderma, LEO, Loreal
7	Payment for manuscript preparation	No	No	No	No
8	Patents (planned, pending or issued)	No	No	No	No
9	Royalties	No	No	No	No

10	Payment for development of educational presentations	No	No	No	No
11	Stock/stock options	No	No	No	No
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	No	NA
13	Other (err on the side of full disclosure)	No	No	No	No

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	No

## Conflicts of interests

### Guidelines for the management of actinic keratoses (Eggert Stockfleth et al.)

The Work Under Consideration for Publication					
		<b>Rino Cerio</b>	<b>Wolfram Sterry</b>	<b>Eggert Stockfleth</b>	
1	Grant	No	No	No	
2	Consulting fee or honorarium	No	No	Abbott, Almirall, ITM, Leo, Meda, Moberg, Spirig	
3	Support for travel to meetings for the study or other purposes	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
4	Fees for participation in review activities, such as data monitoring boards, statistical analysis, end point committees, and the like	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
5	Payment for writing or reviewing the manuscript	No	No	No	
6	Provision of writing assistance, medicines, equipment, or administrative support	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
7	Other	No	No	No	

\* This means money that your institution received for your efforts on this study.

Relevant financial activities outside the submitted work					
1	Board membership	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
2	Consultancy	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
3	Employment	No	No	No	
4	Expert testimony	No	No	No	
5	Grants/grants pending	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
6	Payment for lectures including service on speakers bureaus	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
7	Payment for manuscript preparation	No	No	No	
8	Patents (planned, pending or issued)	No	No	No	
9	Royalties	No	No	No	
10	Payment for	No	No	Abbott, Almirall,	

	development of educational presentations			ITM, Leo, Meda, Spirig	
11	Stock/stock options	No	No	No	
12	Travel/accommodations/meeting expenses unrelated to activities listed**	No	No	Abbott, Almirall, ITM, Leo, Meda, Spirig	
13	Other (err on the side of full disclosure)	No	No	No	

\* This means money that your institution received for your efforts.

\*\* For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Other relationships					
1	Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?	No	No	No	

Guidelines  
For the Management of  
Actinic Keratoses

Stockfleth E, Terhorst D, Braathen L, Cribier B, Cerio R, Ferrandiz C, Giannetti A, Kemeny L,  
Lindelof B, Neumann M, Sterry W, Kerl H

on behalf of the European Dermatology Forum

Table of contents

- 1 Definition and Pathogenesis
- 2 Epidemiology and Risk Factors
- 3 Clinical aspects
- 4 Histopathology
- 5 Treatment options
  - 5.1 Overview
  - 5.2 Ablative procedures (surgical excision and curettage, cryotherapy)
  - 5.3 Topical treatment (5-fluorouracil, imiquimod, diclofenac in hyaluronic acid gel photodynamic therapy, improvements of known concepts for AK)
  - 5.4 Novel topical drugs for the treatment of AK
  - 5.5 Treatment in organ transplant recipients
  - 5.6 Other treatments (systemic retinoids, topical retinoids, dermabrasion, chemical peels, laser, radiotherapy)
- 6 Prevention
- 7 Summary of Recommendations
- 8 References
- 9 Attachment



## 1 Definition and Pathogenesis

Actinic keratoses (AKs) are defined as keratotic macules, papules or plaques with superficial scales on a red base, occurring on areas extensively damaged through sunlight. They should be classified as in situ squamous cell carcinomas (SCCs) (Ackerman, 2003; Heaphy and Ackerman, 2000). Histopathologically an intraepidermal proliferation of atypical keratinocytes can be observed. Clinical studies have established that between 0.025 and 16% of AKs progress to invasive SCCs, with extrapolation studies suggesting the risk of progression at approximately 10% (Glogau, 2000).

AKs are mainly caused by non-ionising radiation, especially through ultraviolet light associated with chronic sun exposure. While UV-A (320 - 400 nm) induced photo-oxidative stress indirectly induces characteristic DNA mutations, the spectrum of UV-B (290 - 320 nm) irradiation directly results in the formation of cyclobutane (thymine) dimer formation in DNA and RNA. In the absence of appropriate repair mechanisms, these DNA changes represent the initiation of keratinocyte mutations which can progress into the development of AKs (Brash et al., 1996).

Other factors like repeated iatrogenic exposure to UV-A, with or without combination with psoralenes, X-rays or radioisotopes are known to induce AKs.

Human papilloma-viruses (HPVs) play a role as co-carcinogen in the etiopathogenesis of AKs (Lober and Lober, 2000; Stockfleth et al., 2004a). The association between cutaneous HPV types and skin carcinogenesis is well known since 1978 in patients with epidermodysplasia verruciformis (Orth et al., 1978). In AKs, cutaneous HPV types and rarely genital types have been detected (Harwood and Proby, 2002). Tumour-inducing effects have been shown for viral E6 protein of cutaneous HPVs. E6 interacts with pro-apoptotic Bak-protein and therefore inhibits apoptosis (Jackson and Storey, 2000; Jackson et al., 2000). A newer study examined the relationship among sun exposure, HPV and the development of AKs. Although the presence of HPV-DNA in eyebrow hair follicle cells had only a small

independent association with AKs, HPV infection is a potentiation of the effect of established risk factors such as advanced age, high sun exposure and fair skin (McBride et al., 2007).

AKs can occur as single lesion or affect an entire field such as sun exposed areas on the forehead or the back of the hand, this occurrence is known as field cancerisation (Braakhuis et al., 2003). After acquiring genetic alterations a stem cell initially forms a clonal unit of dysplastic cells. This dysplastic patch may take place in short order following the initial genetic alteration or might follow years later. The primarily horizontal expansion to an expanding dysplastic field is the next step towards malignancy. Field cancerisation has been seen in almost all epithelial surfaces including e.g. the lung, cervix, breast and colon (Braakhuis et al., 2005).

Cancer-related molecular alterations are found in both AKs and SCCs. This genetic link supports the malignant nature of AKs from its inception. The transformed keratinocytes show a high mutation rate of the tumour-suppressor gene p53 and expression of telomerase (Callen et al., 1997; Mittelbronn et al., 1998). Additionally, the similar chromosomal aberrations have been described for invasive SCC and AK (Ashton et al., 2003).

## **2 Epidemiology and Risk Factors**

Since the 1960s, the average annual increase of NMSC in white populations in Europe, the United States, Canada and Australia has been 3% to 8%. An increase of NMSC is seen in every single country where records exist (Diepgen and Mahler, 2002). In a recent report from the Netherlands, the annual incidence of NMSC has increased rapidly over the past few decades, being 1,2% in men and 3,4% in women for SCC only (de Vries et al., 2006). The exact number of people with BCC and SCC, however, is unknown because in most countries these cancers are not reported in cancer registries (Trakatelli et al., 2007; Lucas et al., 2006.).

Epidemiological data show a high occurrence rate of AKs in populations with skin phototype I-III and a worldwide increase of AKs in the last decades.

In Europe a prevalence of 15 % in men and 6 % in women has been documented in a report from the U.K. Over the age of 70 years, 34 % of males and 18 % of females were found to have AKs (Memon et al., 2000). The highest prevalence rates are found in countries that are both close to the equator and have large fair-skinned populations, such as Australia (Queensland) where rates of AKs over 55 % of men between 30 - 70 and 37 % of women have been reported (Frost et al., 2000). The USA shows prevalence between 11 - 26 % (Salasche, 2000).

In conclusion, the incidence of AKs is increasing such that millions of patients are affected worldwide making AK the most frequent carcinoma in situ in man.

In addition to sex, gender and age, other risk factors concerning the cumulative UV-exposure are known. Geographical factors such as altitude and latitude, increased vocational and recreational sun exposure, a history of severe sunburns in childhood, a sensitive skin phototype of the individual, genetic disorders (xeroderma pigmentosum), and immunodeficiency contribute to the development of AKs (Schwartz et al., 2008). Sex-based differences in occupational and recreational UV- exposure maybe account for the higher prevalence of AKs in men than in women, particularly in younger adults (Anwar et al., 2004). Clinically the affected individual often presents with the characteristic signs of dermatoheliosis such as freckles, solar lentigines and rhytides. A study evaluating patients' history of sunburns, sunbathing, and time spent outdoors, saw a correlation of cumulative, but not intermittent, sun exposure and AKs. (Karagas et al., 2007). In truck drivers with driving experience of more than 40 years, more AKs have been found on the driver side (Kavak et al., 2008).

High-risk-AKs occur mainly in immunosuppressed patients (Schmook and Stockfleth, 2003). Organ-transplanted patients have a 250 fold higher risk to develop AKs and a 100 fold higher risk to develop invasive SCCs (Stockfleth et al., 2002; Ulrich et al., 2002). While about 40 % of immunosuppressed patients develop an invasive SCC only approximately 10 % of immunocompetent patients with AKs show this progression (Glogau, 2000; Stockfleth et al., 2002).

### **3 Clinical aspects**

Typical AKs are skin-coloured to reddish-brown scaly macules, papules or plaques occurring in areas of chronic sun exposure, especially on face, forehead, scalp, ears, neck, décolleté, arms, dorsum of hands and lower lips. Lesions size ranges from a few millimetres up to two centimetres or more in diameter. AKs rarely develop as solitary lesions; in fact multiple lesions are commonly present (field cancerisation). On the lips, AKs can present as actinic cheilitis with dryness, atrophy, and scaly lesions (Cavalcante et al., 2008). A clinical classification is illustrated in Table 1.

Table 1: Clinical classification \*)

- Keratotic
- Atrophic
- Cornu cutaneum
- Verrucous
- Pigmented
- Lichenoid

\*) Overlapping between subtypes may be observed

No distinct clinical boundaries exist between AKs and SCCs. It has been reported that before AKs progress to invasive SCCs, they may become inflamed and painful (Berhane et al., 2002). A systematic review of the literature was undertaken in order to obtain practical clinical parameters to indicate those AKs that are at risk of becoming invasive. Major clinical parameters found - often grouped under the acronym IDBREU – were: I (Induration /Inflammation), D (Diameter > 1 cm), B (Bleeding), R (Rapid Enlargement), E (Erythema) and U (Ulceration). Minor criteria were pain, palpability, hyperkeratosis, pruritic lesions and pigmentation (Quaedvlieg et al., 2006).

One study observed patients with the histopathologically confirmed diagnosis of an AK at the same site as a subsequently developed SCC. The data suggest that of the estimated 10% of AKs that will develop into an SCC, the progression will take approximately 2 years (Fuchs et al., 2007).

Diagnosis of AKs is based upon the typical clinical aspects. Histological confirmation is necessary when clinical doubts exist. A biopsy which includes the dermis is required if deeper involvement needs to be excluded. Dermoscopy can be helpful in the differential diagnosis of pigmented AKs vs. lentigo maligna melanoma and superficial and/or pigmented basal-cell carcinoma. Other techniques, including confocal scanning laser microscopy, have been utilised in serial clinical investigations and have reached a high evidence level. Compared to histology, confocal scanning laser microscopy reached a sensitivity and specificity of nearly 98% and could therefore be considered as a new non-invasive established technique in diagnosing AK and field cancerisation (Ulrich et al., 2007). Other new techniques such as the optical coherence tomography and high frequency ultrasound show promising first results in detecting AKs (Korde et al., 2007; Mogensen and Jemec, 2007).

#### **4 Histopathology**

AKs have been recognized as precursors of cancer or as precancerous lesions in the past. An ongoing lively discussion about its classification and definition shows that on histopathologic grounds alone, AK fulfils all criteria for SCC, thus being a very superficial SCC. AK and SCC are indistinguishable in the epidermal layer (Ackerman and Mones, 2006). The histological criteria of AKs are summarized in Table 2.

Table 2: **Histopathological features**

##### Early lesions

- Focally atypical keratinocytes (large pleomorphic nuclei, hyperchromatic nuclei) in the basal layer of the epidermis
- Crowding of nuclei

- Neoplastic cells spare both acrosyria and acrotrichia
- Alternation of ortho- and parakeratosis
- Actinic elastosis

Fully developed lesions

- Hyperplasia (or sometimes atrophy) of the epidermis
- Rete ridges arranged in buds or columns
- Alternation of ortho- and parakeratosis
- Atypical epidermal keratinocytes involve mostly the lower half of the epidermis. Sometimes with focal involvement of the entire thickness of the epidermis
- Atypical keratinocytes extend along adnexal epithelia
- Dyskeratotic cells and mitotic figures
- Actinic elastosis
- Lymphocytic infiltrate of variable density

The lichenoid subtype of AK is accompanied by dense band-like infiltrate of lymphocytes in the stratum papillare. Acantholytic dyskeratotic cells above suprabasal clefts are found in acantholytic AKs. Other histological types, modelled on the clinical types, are hypertrophic, bowenoid and pigmented (Roewert-Huber et al., 2007b).

The degree of intraepidermal involvement by keratinocytic atypia is graded as mild (AK I), moderate (AK II) or severe (AK III). In grade I the atypical keratinocytes are found in the basal and suprabasal layer, whereas in grade II atypical keratinocytes extend to the lower two-thirds of the epidermis, whereas in grade III full thickness atypia of the epidermis is found, which is equivalent of changes previously called SCC in situ (Röwert-Huber et al., 2007a).

The classification of AKs takes into consideration that AK is an early stage of cancer and that both, AKs and SCCs are stages in the evolution of a continuous process characterised by the proliferation of atypical keratinocytes. Both contain atypical keratinocytes with loss of polarity, nuclear pleomorphism, disordered maturation, and increased numbers of mitotic figures (Ackerman, 2003). AKs and SCCs are frequently contiguous with one another. It is important to emphasize that in a study of >1000 SCCs on sun-damaged skin nearly 100% of these lesions contained histopathologic changes of AK at the periphery (Guenther et al., 1999).

## **5 Treatment options**

## 5.1 Overview

It is impossible to predict for sure which AK will become thicker or more invasive with a potential for destructive growth and risk for metastases, i.e. develop into metastatic squamous cell carcinomas. AKs should therefore be treated. In the decision which therapy should be chosen the following factors play a major role: duration and course of lesions, localisation and extend of disease, solitary or multiple AKs, age, co-morbidity, mental condition and compliance of the patient, pre-existing (skin) cancer and the presence of other risk factors (especially immunosuppression). An exemplary probe biopsy for histological diagnosis may be indicated before therapy.

Currently, there are numerous therapeutic approaches to treat AKs, including both ablative procedures (surgery, laser ablation, curettage, cryosurgery) mainly addressed to treat individual or single lesions and a number of topical treatments (Photodynamic therapy, 5-FU, diclofenac 3%gel and imiquimod) directed to treat both individual lesions and the field. Studies on the frequency and cost of AK treatment in Europe are missing, but a study from the US notes that destructive therapies are effective and remain the standard of care in cost control in the US (Warino et al., 2006).

The areas of field cancerisation account for much of the skin cancer-related morbidity and mortality in organ transplant recipients (OTR) and have become a key target of most dermatological initiatives to reduce the skin cancer burden in OTR. Primarily destructive therapies of individual AKs with surgery, cryosurgery, curettage or laser will not prevent new cancers from emerging in adjacent dysplastic tissues. Management strategies that counteract the effects of systemic immunosuppression via the induction of a locally restricted, tumour-specific immune response, the induction of apoptosis in dysplastic keratinocytes or the use of phototoxic agents can provide the advantage of treating large areas of clinical and subclinical lesions in UV-exposed skin. Topically applied imiquimod, photodynamic therapy and diclofenac 3% gel are promising non-invasive alternative treatment modalities which are applicable to treating larger areas of field cancerisation.

## 5.2 Ablative procedures

### **Surgical excision and Curettage (Strength of recommendation D, quality of evidence IV)**

Excision of AKs is not routinely used and only chosen if invasive SCC is suspected with the need for a histological diagnosis. Shave excision and curettages are frequently used for AK (Emmett und Broadbent, 1987). A curettage specimen may make it difficult to determine whether a lesion is invasive and makes it an unacceptable treatment if SCC is assumed (Motley et al., 2002). There are no trials of surgical therapy for AKs.

## **Cryosurgery (Strength of recommendation A, quality of evidence II)**

Cryosurgery is a widely utilized and effective treatment for single AKs. Cryosurgery refers to use of a cryogen to lower the temperature of the skin and produce cell death. Most commonly liquid nitrogen is sprayed or simply dabbed on the diseased tissue. Cryosurgery is barely standardised concerning frequency, duration, intensity and definitive specification of temperature in the frozen tissue. As a non-specific technique, cryosurgery destroys atypical, but also normal cells by disruption and separation of the epidermis from the dermis. Extensive cryosurgery over large areas has been referred to as cryopeeling and can be used for treating fields of AKs and background damage (Chiarello et al., 2000). Cryosurgery may be quickly performed in an office-based setting, is cost effective and well tolerated by patients (Kalivas, 1996; Zouboulis and Röhrs, 2005).

The efficacy of liquid nitrogen was demonstrated in several studies showing cure rates from 67 – 99%. Cosmetic outcomes in non pigmented skin have been described as very good to excellent, side effects being only mild (Lubritz et al. 1982; Thai et al., 2004; Zouboulis and Röhrs, 2005). The length of thaw correlates to the effectiveness of therapy, but also to possible side effects as hypopigmentation and scarring (Thai et al., 2004).

Several prospective, randomized studies were conducted comparing cryosurgery with PDT showing slightly higher efficacy results for cryosurgery ranging from 69 – 88% complete response rates for cryosurgery vs 52 – 91% in PDT (Szeimies et al., 2002; Freeman et al., 2003; Kaufmann et al., 2008; Morton et al., 2006). PDT however, was judged to show better cosmetic outcomes and higher patient preference (Kaufmann et al., 2008; Morton et al., 2006). After one year, the recurrence rate of initially cleared lesions was 72% in the group of cryosurgery (Krawtchenko et al., 2007).

Cryosurgery has been described in combination with topical 5-FU, where the duration of treatment and consequent side-effects of both modalities could be reduced while maintaining efficacy (Abadir et al., 1983). After six months, more patients treated with cryosurgery following 5-FU applications remained clear of AKs patients treated with cryosurgery alone (30% vs 8%). The high occurrence rate of AK lesions at six months suggests a need for follow-up (Jorizzo et al., 2004).

Most frequent side effects are local pain during and shortly after treatment and pigmentary changes and scar formation. Thick lesions may respond less well than thin lesions, and AKs on the dorsum of the hand may also be more resistant to liquid nitrogen. The cryosurgical results are dependent on the attending physician.

## **5.3 Topical treatment**

### **Topical 5 % -fluorouracil (Strength of recommendation B, quality of evidence II)**

5-fluorouracil (5-FU) is a topical chemotherapeutic antimetabolite that destroys clinical foci via interference with DNA and RNA by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid. The lack of DNA synthesis, particularly in fast-growing dysplastic cells, prevents cell proliferation and causes cell death. 5-FU can be used for the treatment of multiple lesions and is applied twice a day. 2–4 weeks of treatment usually suffice to produce the extensive erosions required to eradicate AKs. It takes 4-6 weeks for the skin to progress through the whole procedure erythema, blistering, necrosis with erosion, and reepithelialization. These effects may cause life-risk complications if dihydropyrimidine-dehydrogenase- deficiency exists (Johnson et al., 1999). One small study compared 4 times daily application of 5FU to 2 times daily and showed no advantages of the more frequent treatment (Epstein, 2006). Another study showed that daily application of 5% 5-FU cream leads to more inflammation but is also more effective than weekly application at clearing AKs from the scalp and face. Our results also suggest that inflammation is likely to be required to achieve a therapeutic effect (Jury et al., 2005).

For localised disease, total clearance rates of approximately 50 % and recurrence rates up to 55 % have been reported with 5-FU (Gupta, 2002; Lawrence et al., 1995; Levy et al., 2001).

An average efficacy rate of  $52 \pm 18\%$  (n = 6 studies, 145 subjects) was shown for 5-FU, vs.  $70 \pm 12\%$  for imiquimod (n = 4 studies, 393 subjects). The results of this meta-analysis show that both imiquimod and 5-fluorouracil are effective methods for the treatment of AKs with imiquimod seeming to have higher efficacy than 5-fluorouracil for AKs located on the face and scalp (Gupta et al., 2005). A recent study showed 96% initial clinical clearance and 67% histological clearance in patients treated with 5-FU. However, the recurrence rate was high after 12 months. The sustained clearance rate of initially cleared individual lesions was 54% and of the total treatment field was 33% of patients after 5-FU (Krawtchenko et al., 2007).

Topical 5-FU can result in severe dermatitis persisting for the entire duration of the treatment with wound infections, pruritus, pain and ulceration with scarring. Phototoxicity as well as contact dermatitis have been described (Meijer et al., 2007). The inflammation induced can be severe, sometimes resulting in patients stopping before adequate treatment has occurred, primarily on the face a combined method with a corticosteroid cream is used. A 0.5 percent preparation of 5-FU is now available. Once daily application is associated with minimal systemic absorption and is better tolerated than higher strength preparations (Levy et al., 2001).

### **Imiquimod 5 % (Strength of recommendation A, quality of evidence I)**



Imiquimod, a member of the class of Immune Response Modifiers, is a toll-like receptor 7-agonist and stimulates the immune response by induction, synthesis and release of cytokines. These cytokines increase the cellular immunity. Therefore it has an indirect antiviral and antineoplastic potency (Miller et al., 1999; Hemmi et al., 2002). Several investigators observed that the number of visible AK lesions augmented during the initial phases of the treatment. This increase is seen as a result of the appearance of subclinical lesions rather than the formation of new AK lesions. The fact that imiquimod effectively uncovers and treats subclinical lesions is considered an additional benefit of treatment with the drug. The clearance of AK was more common among patients with severe local reactions suggesting that inflammation at the site of treatment is part of the mechanism of action of imiquimod in AK (Gupta et al., 2005).

Response rates show complete remission in 84%; a recurrence rate of 10% within 1-year follow up and 20% within 2-years follow up (Stockfleth et al., 2002b; Stockfleth et al., 2004b, Falagas et al., 2006).

A meta-analysis of five randomized trials (n = 1293) found that treatment with imiquimod resulted in complete resolution of AKs in 50% of patients compared to 5% with the control vehicle. The number needed to treat (NNT) for one patient to have their keratosis completely cleared after 12–16 weeks was 2.2 (95% confidence interval 2.0–2.5). For partial (>75%) clearance the NNT was 1.8 (1.7–2.0). Imiquimod 5% cream is effective in the treatment of AK, preventing potential development of squamous cell carcinoma (Hadley et al., 2006).

There have been two randomized- controlled trials with regimens of three times per week for 16 weeks and follow up 8 weeks later. These have classified responses in terms of complete or partial (> 75%) clinical clearance or histological clearance. Complete and partial clearance rates for imiquimod- treated patients (48 -57% and 64-72%, respectively) were clinically and statistically significantly higher than for vehicle-treated patients (2-7% and 4-14%, respectively). The median percentage reduction of baseline lesions was 87% for the imiquimod-treated group and 14% for the vehicle-treated group (Korman et al., 2005; Szeimies et al., 2004; Falagas et al., 2006)

A randomised, double-blind, placebo-controlled study in 436 patients with AKs showed a complete resolution of all lesions in 45% (vs. 3% placebo) and a partial reduction of AKs in 59% (vs. 12% placebo) after a treatment period of 16 weeks (twice per week) The median percent reduction in AK lesions was 83% for the imiquimod group and 0% for the vehicle group (Lebwohl et al. 2004).

A cumulative meta-analysis included ten studies comparing the efficacy of topical agents imiquimod and 5-FU. The average efficacy rate was 52% (n = 6 studies, 145 subjects) for 5-FU and 70% (n = 4 studies, 393 subjects) for imiquimod. This analysis suggests that

imiquimod has higher efficacy than 5-FU for AK lesions located on the face and scalp (Gupta et al., 2005).

A recent study in AK patients comparing imiquimod, 5-FU and cryosurgery showed respectively 85%, 96% and 68% initial clinical clearance and 73%, 67% and 32% as histological clearance in patients treated. However, the recurrence rate was significantly lower for imiquimod after 12 months than for the other treatments where the sustained clearance rate of initially cleared individual lesions was 73%, 54% and 28% for imiquimod, 5-FU and cryosurgery respectively. Also the 12-month sustained clearance for the total treatment field was 73%, 33% and 4% of patients respectively for imiquimod, 5-FU and cryosurgery. Imiquimod treatment of AK resulted in superior sustained clearance in a 12 months follow-up period having a superior cosmetic outcome compared with cryosurgery and 5-FU (Krawtchenko et al., 2007).

Three studies have been conducted in order to evaluate shortened treatment times. Treatment with imiquimod 5% took place three times per week for 4 weeks (course 1) followed by a 4 week post-treatment period. Patients with AK lesions remaining in the treatment area underwent a second 4-week treatment course. Overall, the complete clearance rate was 54- 69% (571/829) and the partial clearance rate (> 75% reduction of AK lesions) was 61 - 80%. The overall complete clearance rate after either course 1 or course 2 is similar to the clearance rate seen after 16 weeks of treatment. The short treatment has the advantage of lower drug exposure, resulting in a better benefit–risk profile for the patient (Stockfleth et al., 2007; Jorizzo et al., 2007; Alomar et al., 2007).

After a median follow-up period of 16 months, 25% (19 of 77) of the patients administered imiquimod three times per week and 43% (23 of 54) of the patients administered imiquimod two times per week had a recurrence of AK in the original treatment area. There were no long-term safety issues, and the skin quality seen in the imiquimod-treated patients at the end of the phase III studies was maintained (Lee et al., 2005).

Topically applied imiquimod causes a local skin reaction, severe erythema (31%), scabbing and crusting (30%), and erosions or ulceration (10%) (Szeimies et al., 2004). In another study, severe erythema was reported by 18% of participants who received imiquimod and 2% of participants who received the vehicle. Side effects could be very different between patients. Overall, imiquimod was very well tolerated (Lebwohl et al., 2004). Only very minimal systemic absorption and good safety margins for topical imiquimod were seen with doses as high as 75 mg three times per week for 16 weeks (Harrison et al., 2004).

**Diclofenac in hyaluronic acid gel (Strength of recommendation A, quality of evidence I)**

Diclofenac is a nonsteroidal anti-inflammatory drug that inhibits cyclooxygenase 2 and thus the upregulation of the arachidonic acid cascade and the production of prostaglandins. Prostaglandin E2 suppresses the production of immune-regulatory lymphocytes, T-and B-cell proliferation and the cytotoxic activity of natural killer cells. In addition to having anti-inflammatory activities, nonsteroidal anti-inflammatory drugs also inhibit neoplastic cell proliferation by inducing apoptosis (Fecker et al, 2007). In a recent publication it was demonstrated that extrinsic apoptosis pathways are of particular importance for AK due to their role in keratinocyte homeostasis and in an immune response. The data demonstrate that a main action of diclofenac/HA in epithelial skin cancer cells is the enhancement of death ligand-mediated, extrinsic apoptosis pathways. This correlated with downregulation of c-FLIP isoforms by diclofenac/HA treatment. Thus, the therapeutic effects of diclofenac/HA may result from a sensitization of neoplastic keratinocytes for an immune response, somehow relating and possibly complementing the effects of Toll-like receptor-7/8 agonists, which directly enhance the immune response. Common principles of topical AK treatments may thus be concluded (Fecker et al., 2010).

Furthermore activation of COX-2 has implications for tumour angiogenesis through up-regulation of vascular endothelial growth factor, which is a potent angiogenic factor required for tumor growth and metastases (Jung et al., 2003). NSAIDs have also been demonstrated to activate peroxisome proliferator-activated-receptor-gamma (PPAR-gamma) which decreases cancer cell proliferation. Topical diclofenac is applied in hyaluronic acid (HA).

Several randomised, double blind, HA gel vehicle-controlled clinical studies have evaluated the efficacy of topical diclofenac HA gel in patients with AK.

After 60 days of treatment, 33% of the target lesions have been cleared in the verum group versus 10% in the placebo group (Rivers et al., 2002). In another study after 90 days of treatment, a complete resolution of 50% was seen in the verum group vs. 20% of those treated with vehicle alone (Wolf et al., 2001).

Assessment was limited to 30 days post-treatment in both studies. These data provide indication of moderate efficacy with low morbidity in mild AKs. A meta-analysis of three randomized trials (n = 364) found that treatment with diclofenac gel resulted in complete resolution of AKs in approximately 40% of patients as compared with 12% with placebo (Pirard et al., 2005).

One study reassessed existing studies using a  $\geq 75\%$  lesion clearance rate demonstrating that diclofenac 3% gel is an effective treatment for the management of AKs. The  $\geq 75\%$  clearance rate of target lesions 30 days after the end of the treatment was then 71% compared to 48% in the placebo group (Rivers and Wolf, 2007). Histological clearance and recurrence rates are not available.

Adverse effects were skin related and mild to moderate in severity (pruritus, erythema, dry skin, hyp- and paraesthesia). Photoallergic reactions have been described, as well as cases of allergic contact dermatitis (Kowalick et al., 2006). Twice daily treatment with diclofenac gel appears to be significantly better tolerated than twice daily application of 5-FU, although it may be somewhat less effective (Smith et al., 2006).

Systemic bioavailability of diclofenac was demonstrated to be considerably lower after topical application than after systemic administration and the drug demonstrated a good safety profile.

### **Photodynamic therapy (strength of recommendation A, quality of evidence I)**

Topical photodynamic therapy (PDT) acts through the selective destruction of atypical keratinocytes (depth of penetration 3-4 mm) through light activation of a photosensitiser in the presence of oxygen. The neoplastic cells accumulate more photosensitiser than normal cells. The photosensitiser generates reactive oxygen species upon illumination, which results in selective photochemical and photothermal effects on the irradiated tissue.

The most commonly used precursors of protoporphyrin IX are 5-aminolevulinic acid (ALA) and its derivatives like the lipophilic agent methyl aminolevulinate (MAL). Both ALA-PDT and MAL-PDT result in significant reduction in scalp AK with no significant difference in efficacy. However, ALA-PDT is more painful than MAL-PDT in the treatment of extensive scalp AK, while MAL is significantly more expensive than ALA (Moloney and Collins, 2007). Usually, superficial crust or keratin is first removed with curettage and the photosensitizing cream is then applied under occlusion for 3 h before illumination with high intensity red light. A variety of incubation times, treatment protocols and light sources were used in the numerous studies; the optimal standards for irradiance, wavelength and dose for the treatment of AKs have yet to be established (Morton et al., 2002; Braathen et al., 2007).

A body of evidence now exists to support the use of PDT for the treatment of AK, including four phase III randomized controlled MAL-PDT studies (Szeimies et al., 2002; Pariser et al., 2003; Freeman et al., 2003; Tarstedt et al., 2005) and two of ALA-PDT (pooled data published by Piacquadio et al., 2004). These studies show that PDT is highly effective for AK. For two treatment sessions, three-month complete response rates of lesions for MAL-PDT are consistently high at around 90% (Szeimies et al., 2002; Pariser et al., 2003; Freeman et al., 2003). Phase III studies with licensed ALA show that 3-month complete response rates of lesions for ALA-PDT was 91%, and at least 75% of lesions cleared in 89% of patients after 3 months (Piaquadio et al, 2004). In one study of patients with multiple AKs on the face and scalp, 88 % of the lesions completely cleared eight weeks after a single photodynamic treatment with ALA-PDT, compared with 6 % after treatment with vehicle and light (Jeffes et al., 2001). ALA-PDT was shown to be an effective and safe therapy for the

treatment of AKs of the face and scalp in skin types I–V, with an acceptable rate of recurrence of histologically confirmed AKs of 19% over 12 months (E.H. Tschien et al., 2006). An advantage of photodynamic therapy is that it can be used over large areas in a single treatment session. Besides, MAL-PDT also provided a consistently favourable cosmetic outcome, rated as “excellent” or “good” by up to 98% of investigators (Szeimies et al., 2002; Pariser et al., 2003; Freeman et al., 2003). The cosmetic outcome with MAL-PDT was significantly superior to that achieved with cryosurgery after 3 months (96% vs. 81% reported cosmetic outcome as “excellent” or “good”; and 84% vs. 51% showing “excellent cosmetic outcome”).

Two studies comparing PDT with cryosurgery show different results, one showing a higher clearance rate (69% PDT vs. 75% cryosurgery, Szeimies et al., 2002) and one showing a lower clearance rate for cryosurgery (91% PDT vs. 68% cryosurgery; Freeman et al., 2003). Another study found similar response rates for PDT and cryosurgery (69 to 89 % versus 68 to 86 %, respectively). Photodynamic therapy was associated with better cosmetic results than cryosurgery and subjects in the intraindividual comparison significantly preferred PDT (Morton et al., 2006). Cryosurgery appeared to be superior for thicker lesions (PDT response 52% vs. cryosurgery 69%) and lesions of the face and scalp (PDT response 75% vs. cryosurgery 91%). Local adverse reactions were reported by 44% of those receiving PDT and 26% of those given cryosurgery (Freeman et al., 2003). At an intraindividual comparison for multiple AKs on the extremities, MAL-PDT showed inferior efficacy compared with cryosurgery. However, both treatments showed high efficacy, and MAL-PDT conveyed the advantages of better cosmetics and higher patient preference (Kaufmann et al., 2008). Several studies have shown a lower efficacy rate on the forehead in comparison to the face and scalp (Szeimies et al., 1996; Jeffes et al., 1997).

A right/left comparison of AK treatment on the back of the hands by PDT and 5-FU showed a similar response to both therapies, clearing 73% and 70%, respectively. Responses remained similar at 6 months (Kurwa et al., 1999). Kurwa et al. saw the same severity of side effects in both treatments in their 16 patients, in a randomized study involving 36 patients, ALA-PDT was better tolerated than 5-FU in the treatment of AK (Smith et al., 2003).

PDT was generally well tolerated by patients. The most important side effect in the majority of patients is pain (severe burning sensation), particularly intense in the forehead, occurring quickly after starting illumination. The pain usually stops after the treatment but can persist for a couple of days. Negative effects are also risk of photosensitivity (mainly for ALA) and time delay between application of cream and starting illumination. Other side effects also include erythema and edema, which resolves within 24 to 48 hours and leaves crusting which will disappear in 1 week. Hypo- or hyperpigmentation can occasionally occur. Some

cases of contact dermatitis to Metvix® have been described (Hohwy T. et al., 2007, Jungersted JM et al, 2008).

Photodynamic therapy (PDT) is increasingly used for treatment of actinic keratoses (AKs) but is a cumbersome procedure. A thin self-adhesive patch (PD P 506 A) containing 5 aminolaevulinic acid (5-ALA) was developed to facilitate PDT. Two separate confirmatory randomized parallel-group phase III studies were set up. In total, 449 patients with up to eight mild to moderate AK study lesions located on the head were treated in 29 German study centres (study AK03: 103 patients; study AK 04: 346 patients). Results Twelve weeks after treatment, 5-ALA patch-PDT proved to be superior to placebo-PDT ( $P < 0.001$ ) and cryosurgery ( $P = 0.007$ ). Efficacy rates on a lesion basis were 82% (AK 03) and 89% (AK 04) for PDT, 77% for cryosurgery and 19% (AK 03) and 29% (AK 04) for placebo-PDT. Local reactions at the treatment site occurred in almost all patients treated with 5-ALA patch-PDT or cryosurgery. Headache was the only side-effect not related to the treatment site which occurred in more than one patient (Hauschild A et al., 2008).

On the other hand, the costs of treatment are considerably higher compared to cryosurgery. The cost-effectiveness of PDT is not established but its use is likely to be limited by the cost of the photosensitizing cream.

In the following paragraph novel pharmacologic substances for AK are reviewed and evaluated regarding their efficacy, safety and applicability for AK.

### **Improvements of known concepts for AK**

In the following paragraph novel pharmacologic substances for AK are reviewed and evaluated regarding their efficacy, safety and applicability for AK.

### **Immune-response modifier- Imiquimod 3.75%**

5% Imiquimod represents an established treatment for AK. Although it has shown good efficacy (59-84% complete clearance), a notable inflammatory response occurs during the course of treatment. Although the inflammation usually does not cause any pain, it may be uncomfortable for the patient as the erythema and/or crusting may be clearly visible and may focus attention. Furthermore, the application of the medication and treatment cycle is often difficult for the patient. The drug is available in small packets ("sachets") and should be applied 3 times a week for 4 to 16 weeks (Europe vs. USA) to a maximum area of 25 cm<sup>2</sup>. In Europe a second cycle is initiated if residual AKs are present 4 weeks after end of treatment, requiring a second consultation.

The new topically available formulation of 3.75% Imiquimod has already been FDA-approved for the treatment of AK in the USA. It offers several advantages compared to 5% Imiquimod.

First, it may be applied to larger areas of the skin such as the complete scalp or face. Furthermore, the application scheme is simplified and shortened using an accelerated dosing scheme for 6 weeks (2 weeks twice daily, two weeks of non-treatment, two weeks once daily), resulting in an overall shorter treatment regime. Complete clearance of all AKs (including lesions revealed during treatment: "subclinical AK") was achieved in 36 percent of patients as compared to only 6 percent of those on placebo. Partial clearance (75 percent reduction or greater in AK totals) was achieved in 59 percent of those treated with 3.75% Imiquimod versus 23 percent for placebo. Similar to 5% Imiquimod 3.75% Imiquimod was able to highlight subclinical lesions reflected by an increase of AK counts after the start of treatment in 85% of patients (Hanke CW et al., 2010; Swanson N et al., 2010).

### **Immune-response modifier-Resiquimod**

Resiquimod is a Toll-like receptor 7 and 8 antagonist, which has recently been evaluated for actinic keratoses. Immunomodulatory effects are quite similar to those of Imiquimod (Toll-like 7 antagonist), however Resiquimod leads to activation of myeloid dendritic cells in addition to plasmacytoid dendritic cells and induces more IL-12 and tumour necrosis factor than imiquimod (Gordon KB et al., 2005). In this regard it has been suggested that Resiquimod may have a greater efficacy compared to Imiquimod. A recent phase-II study evaluated the efficacy of Resiquimod for AK in four escalating dosages (0.01%, 0.03%, 0.06% or 0.1%) in a gel topically applied once daily three times a week for 4 weeks to a contiguous 25-cm<sup>2</sup> area with four to eight lesions (Szeimis RM et al., 2006). Patients with persistent lesions received a second course after an 8-week treatment-free interval. Overall complete clearance was achieved in 77.1% (0.01%), 90.3%(0.03%), 78.1%(0.06%) and 85.3% (0.1%) and complete clearance rates after course 1 only were 40.0%, 74.2%, 56.3% and 70.6%, respectively. During course 1, respectively 0%, 13%, 31% and 38% of patients discontinued treatment for adverse events or local skin reactions, for the resiquimod 0.01%, 0.03%, 0.06% and 0.1% groups. Adverse events of severe intensity, including influenza-like symptoms, were reported by 0% (0.01%), 3%(0.03%), 13%(0.06%) and 12%(0.1%) of patients. Overall, the different concentration showed similar clearance rates, but toleration was better in the low concentration groups (0.01% and 0.03%).

### **COX-inhibitors**

Diclofenac in hyaluronic acid currently represents the single topical COX-inhibitor for the treatment of AK. Cyclo-oxygenases (COX) are enzymes which activate the release of several prostaglandins with different biological properties. Of these, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) represents the main mediator of inflammation and tumor growth (Vane JR et al., 2006). Prostaglandins belong to the class of eicosanoids and are ubiquitarily present in most cell

types. Two different classes of COX can be distinguished, COX-1 and COX-2. Whereas COX-1 is constitutively expressed and plays a role in physiological effects such as cytoprotection of gastric mucosa or renal circulation, COX-2 is induced by pro-inflammatory cytokines, growth factors and tumour promoters such as protein kinase C (PKC), mitogen-activated protein kinase (MAPK) and NF- $\kappa$ B (DuBois RN et al., 1998; Smith W et al., 2003). The up-regulation of COX-2 is strongly related to non physiological conditions like inflammation and cancer and high expression of COX-II has been demonstrated in several solid tumours including epithelial skin cancer. In this regard COX-II up-regulation was shown in AK, SCC and BCC (Muller-Decker K et al., 2004). Diclofenac is a COX-1 and -2 –inhibitor which has shown to be effective and save for the treatment of multiple AKs, also in large areas. Complete clearance rate of around 50% have been reported. In this regard, selective COX-2 inhibitors may be more effective in the treatment of AK as they would selectively block the COX-enzyme which is responsible for tumor promotion. So far, no clinical studies are available investigating the efficacy and safety of a topical, selective COX-2-inhibitor.

#### **Topical low-dose 5-FU in combination with salicylic acid**

A 5% formulation of topical 5-FU represents an established treatment for AK and has long been available. However, 5%-FU is not commonly used in clinical practice as it is associated with moderate to severe local side effects that may result in scarring and pigmentary changes. The topical formulation of 0.5% 5-FU is associated with fewer side effects, but is not available in Europe. A recent systematic review of randomized controlled studies for the use of 5 FU have reported a reduction in mean or median number of lesions of 79.5% for 5% 5- FU and 86.1% for 0.5% 5-FU. In the same analysis, complete clearance of 49% has been reported for 5% 5-FU and 34% for 0.5%, respectively. (Askew DA et al., 2009). Salicylic acid represents a keratolytic agent that has long been used for a variety of hyperkeratotic skin diseases. In combination with low-dose (0.5%) 5-FU it may reduce hyperkeratosis of AK and increase penetration of the biologically active substance 5-FU. A pilot study by Schlaak et al. regarding a topical formulation of 0.5% 5-FU in combination with 10% salicylic acid showed good efficacy for the treatment of AK reporting 77% complete clearance of the total lesion count after 84 days of treatment. A large multi-centre study is currently ongoing which investigates the efficacy and safety of this preparation in a large subset of patients. Data will be presented shortly and approval of the combination is expected soon.

#### **5.4. Novel topical drugs for the treatment of AK**

##### **Ingenol mebutate (PEP005)**

Ingenol mebutate (ingenol-3-angelate, formerly PEP005) is a diterpene ester extracted and purified from the plant *Euphorbia peplus* (Ogburn SM et al., 2004) has recently been



evaluated as a topical treatment for AK. Two different antiproliferative mechanisms of action for ingenol mebutate have been described. Initially, it leads to chemoablation by disruption of the plasma membrane and mitochondria resulting in loss of mitochondrial membrane potential and necrosis of altered cells. Furthermore, eradication of residual tumour cells through induction of tumour-specific antibodies and subsequent inflammation induced by pro-inflammatory cytokines has been reported. Release of cytokines leads to massive infiltration of neutrophils which results in cell death (Challacombe JM et al., 2006). Two phase 2a dose-escalation studies have been performed suggesting that application of 0.05% ingenol mebutate gel once daily for 2 days seem to be the favourable concentration and dosing scheme and a subsequent phase 2b study evaluation ingenol mebutate 0.025 and 0.05% against placebo was performed, showing partial clearance rates between 56.0 and 75.4% and complete clearance rates between 40.0 to 54.4% (Anderson L et al., 2009). Common side effects included erythema (97.5%), flaking/scaling (96.3%) and crusting (82.1%). No scarring caused by ingenol mebutate was observed, while hypo- and hyperpigmentation occurred. No treatment-related serious adverse events were observed. The current data supports the applicability of ingenol mebutate for the short-course treatment of AK.

### **5.5. Treatment in organ transplant recipients**

The below mentioned studies show the benefits of topical therapies in organ transplant recipients (OTRs).

#### **Imiquimod 5 % (strength of recommendation A, quality of evidence I)**

Three placebo-controlled studies in renal transplant recipients and one large multicenter study in kidney, heart and liver transplant recipients found imiquimod to be safe when treating areas of field cancerisation not exceeding 100 cm<sup>2</sup> and 2 sachets per application. For all studies published so far on the use of imiquimod in OTR the drug was applied three times per week for 16 weeks.

A randomized, blinded, placebo-controlled study evaluated imiquimod or placebo at 21 high-risk renal transplant recipients (RTR) with skin dysplasia. Of the 14 patients receiving imiquimod 7 patients (1 taking placebo) had reduced skin atypia, 7 patients (none taking placebo) had reduced viral warts and 5 using imiquimod (1 taking placebo) showed less dysplasia histologically. Over a 12 month period, fewer invasive SCCs arose in the imiquimod-treated skin areas than in control areas. The authors concluded that topical 5% imiquimod cream was effective in reducing cutaneous dysplasia in a proportion of RTR and may reduce the frequency of invasive SCC developing subsequently in treated areas of skin. A proportion of RTRs in this study did not react to imiquimod and did not show benefit from

treatment. Whether these were genuine non-responders or whether this non-response was related to the level of systemic immunosuppression is not known (Brown et al., 2005).

A recent multi-centre, placebo-controlled safety and efficacy study performed by the Skin Care in Organ-transplant Patients (SCOPE) research network enrolled 43 patients in 6 European transplant centers. Among patients randomized to imiquimod, the histologically confirmed complete clearance rate was 62% compared to a complete clearance rate of 0% in the vehicle group (Ulrich et al., 2007a). In order to exclude graft rejections induced through the Th1 immune-response of the immune-response modifier imiquimod, all patients were monitored for changes in hematology and serum chemistry. In all studies published to date with imiquimod in OTR, no adverse effect of the IRM on the function of the graft has been observed.

### **Photodynamic therapy (strength of recommendation A, quality of evidence I)**

Two studies have shown MAL-PDT to be effective in the treatment of AK in transplant recipients (Wulf et al., 2006; Dragieva et al., 2004). One of them, an open label intra-patient randomized study, examined the prevention potential of MAL-PDT in 27 renal transplant patients with AK (Wulf et al., 2006). The mean time to occurrence of the first new lesion was significantly longer in treated than control areas (9.6 vs. 6.8 months, treatment difference 2.9 [95% confidence interval 0.2 to 5.5] months,  $p = 0.034$ ). Over 12 months, 62% (16/26) of treated areas were free of new lesions compared with 35% (9/26) in control areas.

In order to evaluate the preventive effect of PDT on the development of new SCC a further randomized-controlled trial with paired observations in 40 organ-transplant recipients was performed (de Graaf et al., 2006). After 2 years of follow-up, no statistically significant difference was found in the occurrence of new SCC between the treated and untreated areas. The number of keratotic skin lesions increased in both, treatment and control, arms. The authors discuss that the transplant-associated impairment of the cutaneous immune surveillance results in a reduced response to PDT in post-transplant compared with sporadic or non transplant-AK. This was supported by a prospective, open, comparative trial with Aminolevulinic acid (ALA) - PDT for AK in 20 immunosuppressed TR and 20 immunocompetent controls. The overall complete response rate at 12 weeks was 8% and 68% in the respective groups ( $P < 0.05$ ) (Dragieva et al., 2004b).

In a recently published open-label, single-centre, randomized study, 8 organ transplant recipients with epidermal dysplasia were treated with either two cycles of topical MAL-PDT or 5-FU cream which was applied twice daily for 3 weeks to a clinically and histologically comparable area. PDT was found to be significantly more effective than 5-FU in achieving complete resolution (89% vs. 11%). Cosmetic outcome and patient preference were also superior in the PDT-treated group (Perrett et al., 2007).

### **Diclofenac in hyaluronic acid gel (strength of recommendation A, quality of evidence I)**

The use of diclofenac 3% gel in OTR was recently evaluated in a small, open-label study on six OTR (3 kidney, 1 liver and 2 heart transplant patients) with histories of multiple NMSCs and extensive AKs. Diclofenac 3% gel used twice daily for 16 weeks showed a 50% complete clearance rate and 83% partial response rate ( $\geq 75\%$  lesion reduction). Patients were treated with diclofenac 3% gel, twice daily for 16 weeks with generally mild local adverse events at the site of application (Ulrich C et al., 2007b).

In a recent published study 32 organ transplant patients were treated with topical Diclofenac in hyaluronic acid gel. Treatment of AK with 3% diclofenac in 2.5% hyaluronic acid or placebo twice daily was conducted over a total of 16 weeks, followed by a final evaluation 4 weeks after last application of the study drug. Biopsies were taken from the treated areas at the final visit to verify clinical clearance. Patients were assessed for safety variables that included adverse events, local skin reactions, laboratory results, dosage of immunosuppressive medication and indication of graft rejection. A 24 months follow up was conducted after the end of treatment. 87% (n= 28/32) of the patients completed the 16 weeks treatment phase and presented for final evaluation 4 weeks after end of treatment. In the diclofenac 3% gel treatment group a complete clearance of AK lesions was achieved in 41% (9/22) compared to 0% (0/6) in the vehicle group. Side effects in most of the patients included a mild erythema and a mild to moderate swelling of the areas treated. No graft rejections or trends for a deterioration of graft function were detected. No meaningful trends were observed in laboratory results. In 55 % of the previously cleared patients, new AK developed in the study area after an average of 9.3 months. None of these patients developed invasive SCC in the study area within 24 months of follow-up (Ulrich et al., 2010).

## **5.5 Other treatments**

### **Systemic retinoids (Strength of recommendation B, quality of evidence II)**

Systemic retinoids have been assessed for their potential role in suppression or treatment of multiple AKs. Early studies employed etretinate and demonstrated in double-blind crossover trials the efficacy of this drug with a reduction of AKs in 85% (Moriarty et al., 1982). One study suggested that the effect of vitamin A in skin cancer prevention is dose dependent (Alberts et al., 2004).

Use of systemic retinoid as low dose acitretin may be justified in very high-risk patients, such as patients with inherited disorders as xeroderma pigmentosum (abnormal repair of UV-induced DNA damage), nevoid basal cell carcinoma syndrome (tumour suppressor gene abnormality) or in organ transplant recipients, where there is a presumed increased risk of progression from AK to SCC (McNamara et al., 2002). Systemic retinoids have been used in

the secondary prevention of AKs in transplant recipients. A 12 month study found that low dose acitretin therapy (20 mg daily) is safe, well-tolerated, and partially effective in chemoprophylaxis of skin cancer (Carneiro et al., 2005).

Anecdotal evidence over the last 20 years suggests that there can be some considerable morbidity employing this treatment. In addition, there may be a rebound effect once the systemic therapy is stopped. However, these effects were not observed at 4 months follow up in the one available report on this subject (Watson, 1986). Common side effects retinoids are increased sensitivity to sunlight, thinning of the skin, erosions and pruritus.

### **Topical retinoids (Strength of recommendation B, quality of evidence II)**

Retinaldehyde is a natural derivative of vitamin A; it has effects similar to retinoic acid (Sass et al., 1996). Besides counteracting the UV-induced vitamin A deficiency of the epidermis, topical retinaldehyde may have an antioxidant effect (Sachsenberg-Studer, 1999; Sorg et al., 2001) and decreases the number of sunburn cells.

Topical tretinoin cream has been studied at different concentrations with a noticeably dose response. Complete clearance of AKs was reported in 55% of subjects treated with 0,3% ointment whereas only in 35% of subjects using 0,1% ointment (Bollag et al., 1970).

Misiewicz et al. undertook a right/left comparison of tretinoin cream with arotinoid methyl sulphone on the face, revealing a reduction of AKs on the tretinoin treated skin by 30,3% after twice-daily use for 16 weeks. After three to nine weeks of usage there was a deterioration of clinical appearance to below baseline before benefit was seen. This reflects potential benefit from currently available formulations of tretinoin (Misiewicz et al., 1991).

Topical retinoids have shown some benefit in the prevention and treatment of AKs. As an example, a nine month study found that adapalene gel (0.1 and 0.3 %) applied daily for four weeks and twice daily thereafter significantly decreased the number of AKs compared with placebo, and also appeared to improve the appearance of photodamaged skin (Kang et al., 2003).

Other publications show that the epidemiological characteristics of AKs were not modified by the application of retinaldehyde and that retinaldehyde has no prophylactic effects on the development of AKs (Campanelli and Naldi, 2002; Humphreys et al., 1996). In a multicentre open trial, published in non peer-reviewed literature, there was a non significant reduction of facial AKs from a mean of 11 to 9 (11% reduction) after 6 months' use of the low dose of 0,05% once or twice daily (Kligman et al., 1991).

Side effects of topically applied retinoids are increased sensitivity to sunlight, erythema, erosions, pruritus and pain.

### **Dermabrasion (Strength of recommendation C, quality of evidence III)**

With dermabrasion, the skin is destroyed to a controlled layer. In an open study of facial dermabrasion, 22 of 23 subjects remained free of AKs for 1 year with the mean period to development of further AKs being 4,5 years (Coleman et al., 1996). The effective treatment of scalp actinic damage and keratoses with dermabrasion has also been reported (Winton et al., 1986). Manual dermabrasion with silicon carbide sandpaper can be combined with trichloroacetic acid peels (Cooley et al., 1997). A weakly controlled comparison of facial AKs treated with a phenolic peel, dermabrasion or topical 5-FU was reported in 1970. All therapies worked initially, but 6 months after treatment patients developed further AKs (Spira et al., 1970). Dermabrasion requires local anesthesia and may leave scarring or epidermal changes.

### **Chemical peeling (Strength of recommendation C, quality of evidence III)**

A chemical peel is a procedure in which a topically applied wounding agent like trichloroacetic acid, alpha-hydroxy acids, zinc-chloride or phenolic acid creates smooth, rejuvenated skin by an organized repair process and exfoliation.

The efficacy of chemical peelings depends on the agent used and is quoted about 84%; recurrence rates within one year after therapy range from 25 - 35%. Chemical peels have been shown to have superior effectiveness, decreased rates of morbidity and a longer disease-free period when compared to 5-fluorouracil (Lawrence et al., 1995; Spira et al., 1970), other trials showed similar efficacy of chemical peels and 5-FU (Hantash et al., 2006; Witheiler et al., 1997). Trichloroacetic acid can be combined with 70% glycolic acid (Tse et al., 1996).

Prior to treatment, patients should be educated about possible complications of stinging or burning sensation, visible peeling (which usually lasts 5 to 7 days), pigment changes, infections, and rarely scarring. Post-treatment sunscreen should be applied (Lawrence et al., 1995).

### **Laser (Strength of recommendation C, quality of evidence III)**

Near infrared laser systems like carbon dioxide (CO<sub>2</sub>) or Erbium-YAG lasers should be successful in treating AKs. Both are ablative laser systems and can be used for single lesions as well as full face resurfacing.

Full face laser resurfacing can provide long-term effective prophylaxis against AKs and may reduce the incidence of AK related SCC (Sherry et al., 2007; Iyer et al., 2004). Complete remission is documented from 90 to 91% with recurrence rates for single lesions ranging from 10 to 15% within 3 to 6 months (Wollina et al., 2001, Yu et al., 2003). Long-term recurrence-free intervals have been seen after laser resurfacing with 44% of the patients having no recurrence during the follow-up period, the mean average being 39 months. 56%

of the patients developed few new lesions after treatment. Of the recurrences, 20% occurred within 1 year and 36% occurred after 1 year (Ostertag et al., 2006a).

One study compared laser treatment to 5-FU, showing more side effects in the laser group but also less recurrences 3, 6 and 12 months after treatment (Ostertag et al., 2006b). Another study demonstrated benefit for AK reduction and NMSC prophylaxis with no significant differences among the three treatment groups, carbon dioxide laser resurfacing, 30% trichloroacetic acid peel, or 5-FU cream (Hantash et al. 2006).

Disappointing results reported in earlier literature maybe related to technical aspects, as the outcomes of full face resurfacing are strongly user dependent (Fulton et al., 1999).

Adverse events are pain, inflammation, pigment changes and scarring as well as delayed healing and postinflammatory erythema (Wollina et al., 2001, Yu et al., 2003).

### **Radiotherapy (strength of recommendation D, quality of evidence II)**

The treatment of AKs with X-rays is considered obsolete due to the cocarcinogenic effect of X-rays.

### **6 Prevention (strength of recommendation A, quality of evidence I)**

Prevention of AKs is an important part in AK-management (Armstrong and Kricger, 2001; Thompson, 1993). Education of patients (UV-protection, self-examination and detection of early lesions) is particularly important. AK is an ongoing disease that requires frequent follow-up (half-yearly to yearly) and long-term management. Avoiding sun exposure and the use of sun block are important aspects of preventing the development of AKs. Sun block has a combined emollient and photoprotective effect. Several studies showed that regularly applied sun block is effective not only in the prevention of AKs but also in the reduction of AKs (Thompson et al., 1993; Darlington et al., 2003; Green et al., 1999; Naylor et al., 1995). In a recent single-centre, matched pairs observational study, a group of 60 organ transplant recipients with daily application of a highly protective, liposomal sunscreen (Daylong actinica®) as part of their rigorous sun prevention behaviour were compared with a control group. Within the duration of the study of 24 months, 42 of the 120 patients developed 82 new lesions of AK (all in the control group). Eight patients of the control group developed new invasive squamous cell carcinomas versus none in the sunscreen group. In the sunscreen group, 102 lesions of AKs went into spontaneous remission. Sun protection measures thus also have a positive impact on the high-risk group of organ transplant recipients (Ulrich C et al., 2008, 2009).

This high-risk group should receive special attention, already before entering the transplant waiting list; at this point all candidates for transplantation ought to receive a skin cancer risk factor-oriented assessment. Posttransplant aftercare needs to be individually adjusted to

prevalent extrinsic and intrinsic risk factors. Although the threshold of skin cancer necessitating revision of the immunosuppressive medication is debated, this measure should be envisaged at the occurrence of NMSC. Ongoing randomized prospective trials assess the burden of new skin tumors, as well as graft and patient survival in patients with NMSC after the introduction of mTOR inhibitors (Ulrich C et al., 2008b).

## **7 Summary of Recommendations**

It has to be declared that the physician who cares about the patient has always to keep in mind the individual needs of the patient. The physician has to respect the individuality of the patient and has to see the guideline as recommendation and supporting device for therapeutical strategies and efforts.

## **8 References**

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

Ackerman AB. Solar keratosis is squamous cell carcinoma. *Arch Dermatol* 2003; 139: 1216-1217.

Ackerman AB, Mones JM. Solar (actinic) keratosis is squamous cell carcinoma. *Br J Dermatol*. 2006 Jul;155(1):9-22.

Alberts D, Ranger-Moore J, Einspahr J, Saboda K, Bozzo P, Liu Y, Xu XC, Lotan R, Warneke J, Salasche S, Stratton S, Levine N, Goldman R, Islas M, Duckett L, Thompson D, Bartels P, Foote J. Safety and efficacy of dose-intensive oral vitamin A in subjects with sun-damaged skin. *Clin Cancer Res*. 2004 Mar 15;10(6):1875-80.

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

Anderson L, Schmiedee GJ, Stough DB et al. Randomized, double-blind, double-dummy, vehicle-controlled study of ingenol mebutate gel 0.025% and 0.05% for the treatment of actinic keratosis. *J Am Acad Dermatol* 2009;60:934-43.

Anwar J, Wrone DA, Kimyai-Asadi A, Alam M. The development of actinic keratosis into invasive squamous cell carcinoma: evidence and evolving classification schemes. *Clin Dermatol*. 2004 May-Jun;22(3):189-96.

Armstrong BK, Kricger A. The epidemiology of UV induced skin cancer. *J Photochem Photobiol B* 2001; 63: 8-18.

Ashton KJ, Weinstein SR, Maguire DJ, Griffiths LR. Chromosomal aberrations in squamous cell carcinoma and solar keratoses revealed by comparative genomic hybridization. *Arch Dermatol* 2003; 139: 876-882.

Askew DA, Mickan SM, Soyewr HP, Wilkinson D. Effectiveness of 5-fluorouracil treatment for actinic keratosis--a systematic review of randomized controlled trials. *Int J Dermatol*. 2009 May;48(5):453-63.

Berhane T, Halliday GM, Cooke B, Barnetson RSC. Inflammation is associated with progression of actinic keratoses to squamous cell carcinomas in humans. *Br J Dermatol* 2002; 146: 810-815.

Bollag W, Ott F. Retinoic acid: topical treatment of senile or actinic keratoses and basal cell carcinomas. *Agents Actions* 1970; 1:172-5

Braakhuis BJM, Tabor MP, Kummer JA, Leemans CR, Brakenhoff RH. A genetic explanation of Slaughter's concept of field cancerization: Evidence and clinical implications. *Cancer Res* 2003; 63: 1727-1730.

Braakhuis BJ, Brakenhoff RH, Leemans CR. Second field tumors: a new opportunity for cancer prevention? *Oncologist*. 2005 Aug;10(7):493-500.

Braathen LR, Szeimies RM, Basset-Seguín N, Bissonnette R, Foley P, Pariser D, Roelandts R, Wennberg AM, Morton CA; International Society for Photodynamic Therapy in Dermatology. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus. *International Society for Photodynamic Therapy in Dermatology*, 2005. *J Am Acad Dermatol*. 2007 Jan;56(1):125-43.



Brash DE, Ziegler A, Jonason AS, Simon JA, Kunala S, Leffell DJ. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor protection. *J Invest Dermatol Symp Proc* 1996; 1: 136-142.

Brown VL, Atkins CL, Ghali L, Cerio R, Harwood CA, Proby CM. Safety and efficacy of 5% imiquimod cream for the treatment of skin dysplasia in high-risk renal transplant recipients: randomized, double-blind, placebo-controlled trial. *Arch Dermatol*. 2005;141:985-93

Callen JP, Bickers DR, Moy RL. Actinic keratoses. *J Am Acad Dermatol* 1997; 36: 650-653.

Campanelli A, Naldi L. A retrospective study of the effect of long-term topical application of retinaldehyde (0.05%) on the development of actinic keratosis. *Dermatology* 2000; 205: 146-152.

Carneiro, RV, Sotto, MN, Azevedo, LS, et al. Acitretin and skin cancer in kidney transplanted patients. Clinical and histological evaluation and immunohistochemical analysis of lymphocytes, natural killer cells and Langerhans' cells in sun exposed and sun protected skin. *Clin Transplant* 2005; 19:115

Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. *J Oral Maxillofac Surg*. 2008 Mar;66(3):498-503.

Challacombe JM, Suhrbier A, Parson PG et al. Neutrophils are a key component of the anti.tumour efficacy of topical chemotherapy with ingenol-3-angelate. *J Immunol* 2006;177:8123-32.

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

Coleman WP 3rd, Yarborough JM, Mandy SH. Dermabrasion for prophylaxis and treatment of actinic keratoses. *Dermatol Surg* 1996; 22:17–21

Cooley JE, Casey DL, Kauffman CL. Manual resurfacing and trichloroacetic acid for the treatment of patients with widespread actinic damage. Clinical and histologic observations. *Dermatol Surg* 1997; 23:373–9

de Rijke JM, Schouten LJ, Hillen HF et al. Cancer in the very elderly Dutch population. *Cancer* 2000; 89:1121–33.

de Vries E, Coebergh JW, van der Rhee H. Trends, causes, approach and consequences related to the skin-cancer epidemic in the Netherlands and Europe. *Ned Tijdschr Geneeskd* 2006; 150:1108–15

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

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

Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br J Dermatol* 2002; 146 (suppl. 61): 1–6

Diffey BL, Langtry JA. Skin cancer incidence and the ageing population. *Br J Dermatol* 2005; 153:679–80

Dragieva G, Prinz BM, Hafner J, Dummer R et al. A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients. *Br J Dermatol* 2004a;151:196–200

Dragieva G, Hafner J, Dummer R et al. Topical photodynamic therapy in the treatment of actinic keratoses and Bowen's disease in transplant recipients. *Transplantation* 2004b;77:1–6

DuBois RN, Abrahamson SB, Crofford L et al. Cyclooxygenase in biology and disease. *FASEB J* 1998; 12:1063-73.

Epstein, E. Twice daily vs. four times daily 5-fluorouracil therapy for actinic keratoses: a split face study *Br Journal of Dermatology* 2006 154, pp774–807

Falagas ME, Angelousi AG, Peppas G. Imiquimod for the treatment of actinic keratosis: A meta-analysis of randomized controlled trials. *J Am Acad Dermatol.* 2006 Sep;55(3):537-8.

Fecker LF, Stockfleth E, Nindl I, Ulrich C, Forschner T, Eberle J. The role of apoptosis in therapy and prophylaxis of epithelial tumours by nonsteroidal anti-inflammatory drugs (NSAIDs). *Br J Dermatol*. 2007 May;156 Suppl 3:25-33.

Fecker LF, Stockfleth E, Rodus PMt, Schwarz C, Eberle J. Enhanced death ligand-induced apoptosis in cutaneous SCC cells by treatment with diclofenac/hyaluronic acid correlates with downregulation of c-FLIP. *J Invest Dermatol* 2010; 130:2098-109

Freeman M, Vinciullo C, Francis D, Spelman L, Nguyen R, Fergin P, Thai KE, Murrell D, Weightman W, Anderson C, Reid C, Watson A, Foley P. A comparison of photodynamic therapy using topical methyl aminolevulinate (Metvix) with single cycle cryotherapy in patients with actinic keratosis: a prospective, randomized study. *J Dermatolog Treat*. 2003; 14: 99-106.

Frost C, Williams G, Green A. High incidence and regression rates of solar keratoses in a queensland community. *J Invest Dermatol* 2000; 115: 273-277.

Fuchs A, Marmur E. The kinetics of skin cancer: progression of actinic keratosis to squamous cell carcinoma. *Dermatol Surg*. 2007 Sep;33(9):1099-101.

Fulton JE, Rahimi AD, Helton P, Dahlberg K, Kelly AG. Disappointing results following resurfacing of facial skin with CO2 lasers for prophylaxis of keratoses and cancers. *Dermatol Surg*. 1999; 25: 729-732.

Glogau RG. The risk of progression to invasive disease. *J Am Acad Dermatol* 2000;42(1 Pt 2):23-4.

Gordon KB, Gorski KS, Gibson SJ et al. Synthetic TLR agonists reveal functional differences between human TLR7 and TLR8. *J Immunol* 2005; 174:1259-68.

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

Guenther ST, Hurwitz RM, Buckel LJ, Gray HR. Cutaneous squamous cell carcinomas consistently show histologic evidence of in situ changes: A clinicopathologic correlation. *J Am Acad Dermatol* 1999; 41: 443-448.

Gupta AK, The management of actinic keratoses in the United States with topical fluorouracil: a pharmaco-economic evaluation. *Cutis* 2002; 70: 30-36.

Gupta AK, Davey V, Mcphail H. Evaluation of the effectiveness of imiquimod and 5-fluorouracil for the treatment of actinic keratosis: Critical review and meta-analysis of efficacy studies. *J Cutan Med Surg*. 2005 Oct;9(5):209-14.

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

Hanke CW, Beer KR, Stockfleth E, Wu J, Rosen T, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily application to the face and balding scalp for two 3-week cycles. *J Am Acad Dermatol*. 2010 Apr;62(4):573-81.

Hantash BM, Stewart DB, Cooper ZA, Rehmus WE, Koch RJ, Swetter SM. Facial resurfacing for nonmelanoma skin cancer prophylaxis. *Arch Dermatol*. 2006 Aug;142(8):976-82.

Harrison LI, Skinner SL, Marbury TC, Owens ML, Kurup S, McKane S, Greene RJ. Pharmacokinetics and safety of imiquimod 5% cream in the treatment of actinic keratoses of the face, scalp, or hands and arms. *Arch Dermatol Res*. 2004 Jun;296(1):6-11.

Harwood CA, Proby M. Human papillomaviruses and non-melanoma skin cancer. *Curr Opin Infect Dis* 2002; 15: 101-114.

Hauschild A , Stockfleth E, Popp G, Borrosch F,. Bruning,H., Dominicus R, Mensing H, Reinhold U, Reich K, Moor, A.C.E. , Stocker,M, Ortland,C, Brunnert M, Szeimies R.-M. Optimization of photodynamic therapy with a novel self-adhesive 5-aminolaevulinic acid patch: results of two randomized controlled phase III studies. . *Br J Dermatol*. 2009 May;160(5):1066-74. Epub 2009 Feb 16

Heaphy MR Jr, Ackerman AB. The nature of solar keratosis: a critical review in historical perspective. *J Am Acad Dermatol*. 2000; 43: 138-50.

Hemmi H, Kaisho T, Takeuchi O, Sato S, Sanjo H, Hoshino K, Horiuchi T, Tomizawa H, Takeda K, Akira S. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat Immunol.* 2002 Feb;3(2):196-200.

Holme SA, Malinowszky K, Roberts DL. Changing trends in nonmelanoma skin cancer in South Wales 1988–98. *Br J Dermatol* 2000; 143:1224–9.

Hohwy T, Andersen KE, Sølvsten H, Sommerlund M. Allergic contact dermatitis to methyl aminolevulinate after photodynamic therapy in 9 patients. *Contact Dermatitis.* 2007 Nov;57(5):321-3.

Humphreys TR, Werth V, Dzubow L, Kligman A. Treatment of photodamaged skin with trichloroacetic acid and topical tretinoin. *J Am Acad Dermatol* 1996; 34: 638-44.

Iyer S, Friedli A, Bowes L, Kricorian G, Fitzpatrick RE. Full face laser resurfacing: therapy and prophylaxis for actinic keratoses and non-melanoma skin cancer. *Lasers Surg Med.* 2004;34(2):114-9.

Jackson S, Storey A. E6 proteins from diverse cutaneous HPV types inhibit apoptosis in response to UV damage. *Oncogene* 2000; 19: 592-598.

Jackson S, Harwood C, Thomas M, Banks L, Storey A. Role of Bak in UV-induced apoptosis in skin cancer and abrogation by HPV E6 proteins. *Genes & Dev* 2000; 14: 3065-3073.

Jeffes EW, McCullough JL, Weinstein GD, Fergin PE, Nelson JS, Shull TF, Simpson KR, Bukaty LM, Hoffman WL, Fong NL. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. *Arch Dermatol.* 1997 Jun;133(6):727-32.

Jeffes, EW, McCullough, JL, Weinstein, GD, et al. Photodynamic therapy of actinic keratoses with topical aminolevulinic acid hydrochloride and fluorescent blue light. *J Am Acad Dermatol* 2001; 45:96

Johnson MP, Hageboutros A, Wang K, High L, Smith JB, Diasio RB: Life threatening toxicity in a dihydropyrimidin-dehydrogenase-deficiency patient after treatment with topical 5-fluorouracil. *Clinical Cancer Research* 1999; 5: 2006-2011.

Jorizzo J, Weiss J, Furst K, VandePol C, Levy SF. Effect of a 1-week treatment with 0.5% topical fluorouracil on occurrence of actinic keratosis after cryosurgery: a randomized, vehicle-controlled clinical trial. *Arch Dermatol*. 2004 Jul;140(7):813-6.

Jorizzo J, Dinehart S, Matheson R et al. Vehicle-controlled, doubleblind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for AK. Update on actinic keratosis in clinical trial experience with Imiquimod *Br J Dermatol*. 2007, 157 (Suppl. 2), 32–33

Jorizzo J, Dinehart S, Matheson R, Moore JK, Ling M, Fox TL, McRae S, Fielder S, Lee JH. Vehicle-controlled, double-blind, randomized study of imiquimod 5% cream applied 3 days per week in one or two courses of treatment for actinic keratoses on the head. *J Am Acad Dermatol*. 2007 Aug;57(2):265-8.

Jung YJ, Isaacs JS, Lee S, Trepel J, Neckers L. IL-1beta-mediated up-regulation of HIF-1alpha via an NFkappaB/COX-2 pathway identifies HIF-1 as a critical link between inflammation and oncogenesis. *FASEB J*. 2003 Nov;17(14):2115-7.

Jungersted JM, Dam TN, Bryld LE, Agner T. Allergic reactions to Metvix (ALA-ME). *Contact Dermatitis*. 2008 Mar;58(3):184-6.

Jury CS, Ramraka-Jones VS, Gudi V, Herd RM. A randomized trial of topical 5% 5-fluorouracil in the treatment of actinic keratoses comparing daily with weekly treatment *Br J Dermatol*. 2005 153, pp808–810

Kalivas J. Cryosurgery of actinic keratoses: the patient's perspective. *Dermatol Surg*. 1996 May;22(5):486.

Karagas MR, Zens MS, Nelson HH, Mabuchi K, Perry AE, Stukel TA, Mott LA, Andrew AS, Applebaum KM, Linet M. Measures of cumulative exposure from a standardized sun exposure history questionnaire: a comparison with histologic assessment of solar skin damage. *Am J Epidemiol*. 2007 Mar 15;165(6):719-26. Epub 2007 Jan 4.

Kaufmann R, Spelman L, Weightman W, Reifenberger J, Szeimies RM, Verhaeghe E, Kerrouche N, Sorba V, Villemagne H, Rhodes LE. Multicentre intraindividual randomized trial of topical methyl aminolaevulinate-photodynamic therapy vs. cryotherapy for multiple actinic keratoses on the extremities. *Br J Dermatol*. 2008 May;158(5):994-9. Epub 2008 Mar 13.

Kligman AL, Thorne EG. Topical therapy of actinic keratoses with tretinoin. In: Retinoids in Cutaneous Malignancy (Marks R, ed.), Oxford: Blackwell Scientific Publications, 1991; 66–73.

Korman N, Moy R, Ling M, Matheson R, Smith S, McKane S, Lee JH. Dosing with 5% imiquimod cream 3 times per week for the treatment of actinic keratosis: results of two phase 3, randomized, double-blind, parallel-group, vehicle-controlled trials. *Arch Dermatol*. 2005 Apr;141(4):467-73.

Kowalzik L, Ziegler H. Photoallergic contact dermatitis from topical diclofenac in Solaraze gel. *Contact Dermatitis*. 2006 Jun;54(6):348-9.

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

Kavak A, Parlak AH, Yesildal N, Aydogan I, Anul H. Preliminary study among truck drivers in Turkey: effects of ultraviolet light on some skin entities. *J Dermatol*. 2008 Mar;35(3):146-50.

Korde VR, Bonnema GT, Xu W, Krishnamurthy C, Ranger-Moore J, Saboda K, Slayton LD, Salasche SJ, Warneke JA, Alberts DS, Barton JK. Using optical coherence tomography to evaluate skin sun damage and precancer. *Lasers Surg Med*. 2007 Oct;39(9):687-95.

Krawtchenko N, Roewert-Huber J, Ulrich M, Mann I, Sterry W, Stockfleth E. A randomised study of topical 5% imiquimod vs. topical 5-fluorouracil vs. cryosurgery in immunocompetent patients with actinic keratoses: a comparison of clinical and histological outcomes including 1-year follow-up. *Br J Dermatol*. 2007 Dec;157 Suppl 2:34-40.

Kurwa HA, Yong Gee SA, Seed P et al. A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. *J Am Acad Dermatol* 1999; 41:414–18

Lawrence, N, Cox, SE, Cockerell, CJ, et al. A comparison of the efficacy and safety of Jessner's solution and 35% trichloroacetic acid vs 5% fluorouracil in the treatment of widespread facial actinic keratoses. *Arch Dermatol* 1995; 131:176.

Lebwohl M, Dinehart S, Whiting D, Lee PK, Tawfik N, Jorizzo J, Lee JH, Fox TL. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol*. 2004 May;50(5):714-21.

Lee PK, Harwell WB, Loven KH, Phillips TJ, Whiting DA, Andres KL, Lee JH. Long-term clinical outcomes following treatment of actinic keratosis with imiquimod 5% cream. *Dermatol Surg*. 2005 Jun;31(6):659-64.

Levy, S, Furst, K, Chern, W. A pharmacokinetic evaluation of 0.5% and 5% fluorouracil topical cream in patients with actinic keratosis. *Clin Ther* 2001; 23:908.

Lober BA, Lober CW. Actinic keratosis is squamous cell carcinoma. *South Med J* 2000; 93: 650-655.

Lubritz RR, Smolewski SA. Cryosurgery cure rate of actinic keratoses. *J Am Acad Dermatol* 1982; 7: 631-632.

Lucas R, McMichael T, Smith W et al. Environmental Burden of Disease Series, No. 13. Solar Ultraviolet Radiation. Global Burden of Disease from Solar Ultraviolet Radiation. Geneva: World Health Organization, Public Health and the Environment, 2006

McBride P, Neale R, Pandeya N, Green A. Sun-related factors, betapapillomavirus, and actinic keratoses: a prospective study. *Arch Dermatol*. 2007 Jul;143(7):862-8.

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

Meijer BU, de Waard-van der Spek FB. Allergic contact dermatitis because of topical use of 5-fluorouracil (Efudix cream). *Contact Dermatitis*. 2007 Jul;57(1):58-60.

Memon AA, Tomenson JA, Bothwell J, Friedmann PS. Prevalence of solar damage and actinic keratosis in a Merseyside population. *Br J Dermatol* 2000; 142: 1154-1159.

Miller RL, Gerster JF, Owens ML, Slade HB, Tomai MA. Imiquimod applied topically: a novel immune response modifier and new class of drug. *Int J Immunopharmacol*. 1999 Jan;21(1):1-14.



Misiewicz J, Sendagorta E, Golebiowska A et al. Topical treatment of multiple actinic keratoses of the face with arotinoid methyl sulfone cream vs. tretinoin cream: a double blind comparative study. *J Am Acad Dermatol* 1991; 24:448–51

Mittelbronn MA, Mullins DL, Ramos-Caro FA, Klowers FP. Frequency of pre-existing actinic keratosis in cutaneous squamous cell carcinoma. *Int J Dermatol* 1998; 37: 677-681.

Mogensen M, Jemec GB. Diagnosis of nonmelanoma skin cancer/keratinocyte carcinoma: a review of diagnostic accuracy of nonmelanoma skin cancer diagnostic tests and technologies. *Dermatol Surg.* 2007 Oct;33(10):1158-74.

Moloney FJ, Collins P. Randomized, double-blind, prospective study to compare topical 5-aminolaevulinic acid methylester with topical 5-aminolaevulinic acid photodynamic therapy for extensive scalp actinic keratosis. *Br J Dermatol.* 2007 Jul;157(1):87-91.

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

Morton CA, Brown SB, Collins S et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol* 2002; 146:552–67.

Morton C, Campbell S, Gupta G, Keohane S, Lear J, Zaki I, Walton S, Kerrouche N, Thomas G, Soto P; AKtion Investigators. Intraindividual, right-left comparison of topical methyl aminolaevulinate-photodynamic therapy and cryotherapy in subjects with actinic keratoses: a multicentre, randomized controlled study. *Br J Dermatol.* 2006 Nov;155(5):1029-36.

Motley R, Kersey P, Lawrence C; British Association of Dermatologists; British Association of Plastic Surgeons; Royal College of Radiologists, Faculty of Clinical Oncology. Multiprofessional guidelines for the management of the patient with primary cutaneous squamous cell carcinoma. *Br J Dermatol.* 2002 Jan;146(1):18-25.

Muller-Decker K. Cyclooxygenases in the skin. *J Dtsch Dermatol Ges* 2004;2:668-75.; Nijsten T, Colpaert CG, Vermeulen PB et al. Cyclooxygenase-2 expression and angiogenesis in squamous cell carcinoma of the skin and its precursors: a paired immunohistochemical of 35 cases. *Br J Dermatol* 2004; 151:837-45.

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

Ogburne SM, Suhrbier A, Jones B et al. Antitumor activity of 3-ingenyl angelate: plasma membrane and mitochondrial disruption and necrotic cell death. *Cancer Res* 2004;64:2833-9.

Orth G, Jablonska S, Favre M, Jarzabek-Chorzelska M, Rzeska G. Characterization of two types of human papillomaviruses in lesions of epidermodysplasia verruciformis. *Proc Nat Acad Sci USA* 1978; 75: 1537-1541.

Ostertag JU, Quaedvlieg PJ, Neumann MH, Krekels GA. Recurrence rates and long-term follow-up after laser resurfacing as a treatment for widespread actinic keratoses on the face and scalp. *Dermatol Surg.* 2006a Feb;32(2):261-7.

Ostertag JU, Quaedvlieg PJ, van der Geer S, Nelemans P, Christianen ME, Neumann MH, Krekels GA. A clinical comparison and long-term follow-up of topical 5-fluorouracil versus laser resurfacing in the treatment of widespread actinic keratoses. *Lasers Surg Med.* 2006b Sep;38(8):731-9.

Pariser DM, Lowe NJ, Stewart DM, Jarratt MT, Lucky AW, Pariser RJ, et al. Photodynamic therapy with topical methyl aminolevulinate for actinic keratosis: results of a prospective randomized multicenter trial. *J Am Acad Dermatol* 2003;48: 227-32.

Perrett CM, McGregor JM, Warwick J et al. Treatment of post-transplant premalignant skin disease: a randomized inpatient comparative study of 5-fluorouracil cream and topical photodynamic therapy. *Br J Dermatol.* 2007;156:320-8

Piacquadio DJ, Chen DM, Farber HF, Fowler JF Jr, Glazer SD, Goodman JJ, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigatorblinded, phase 3, multicenter trials. *Arch Dermatol* 2004;140: 41-6

Pirard, D, Vereecken, P, M&eacut;lot, C, Heenen, M. Three percent diclofenac in 2.5% hyaluronan gel in the treatment of actinic keratoses: a meta-analysis of the recent studies. *Arch Dermatol Res* 2005; 297:185

Quaedvlieg PJ, Tirsi E, Thissen MR, Krekels GA. Actinic keratosis: how to differentiate the good from the bad ones? *Eur J Dermatol.* 2006 Jul-Aug;16(4):335-9.

Rivers JK, Arlette J, Shear N et al. Topical treatment of actinic keratoses with 3,0% diclofenac in 2,5% hyaluronan gel. *Br J Dermatol* 2002; 146:94–100

Rivers JK, Wolf J. Assessing clinically meaningful end points for the management of actinic keratosis with diclofenac 3% gel. *Acta Derm Venereol.* 2007;87(2):188-9.

Röwert-Huber J, Patel MJ, Forschner T, Ulrich C, Eberle J, Kerl H, Sterry W, Stockfleth E. Actinic keratosis is an early in situ squamous cell carcinoma: a proposal for reclassification. *Br J Dermatol.* 2007a May;156 Suppl 3:8-12.

Roewert-Huber J, Stockfleth E, Kerl H. Pathology and pathobiology of actinic (solar) keratosis - an update. *Br J Dermatol.* 2007b Dec;157 Suppl 2:18-20.

Sachsenberg-Studer EM. Tolerance of topical retinaldehyde in humans. *Dermatology* 1999; 199: S61-63.

Salasche SJ: Epidemiology of actinic keratoses and squamous cell carcinoma. *J Am Acad Dermatol* 2000; 42: 4-7.

Sass JO, Didierjean L, Carraux P, Plum C, Nau H, Saurat JH: Metabolism of topical retinaldehyde and retinol by mouse skin in vivo: predominant formation of retinyl esters and identification of 14-hydroxy-4,14-retro-retinol. *Exp Dermatol* 1996; 5: 267-271.

Schmook T, Stockfleth E. Current treatment patterns in non-melanoma skin cancer across Europe. *J Dermatolog Treat* 2003; 14: S3-10.

Schwartz RA, Bridges TM, Butani AK, Ehrlich A. Actinic keratosis: an occupational and environmental disorder. *J Eur Acad Dermatol Venereol.* 2008 May;22(5):606-15.

Sherry SD, Miles BA, Finn RA. Long-term efficacy of carbon dioxide laser resurfacing for facial actinic keratosis. *J Oral Maxillofac Surg.* 2007;65(6):1135-9.

Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R. Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol* 2003;2:629-35.

Smith wI, DeWitt DL, Garavito RM. Cyclooxygenases: structural, cellular and molecular biology. *Ann Rev Biochem* 2000; 69:145-82; Yu W, Murray NR, Weems C et al. Role of Cyclooxygenase 2 in protein kinase C beta II-mediated colon carcinogenesis. *J Biol Chem* 2003;278:11167-74.

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

Sorg O, Tran C, Saurat JH. Cutaneous vitamins A and E in the context of ultraviolet- or chemically-induced oxidative stress. *Skin Pharmacol Appl Skin Physiol* 2001; 14: 363-372.

Spira M, Freeman R, Arfai P et al. Clinical comparison of chemical peeling, dermabrasion, and 5-FU for senile keratoses. *J Plast Reconstr Surg* 1970; 46:61–6

Stockfleth E, Ulrich C, Meyer T, Christophers E. Epithelial malignancies in organ transplant patients: clinical presentation and new methods of treatment. *Recent Results Cancer Res.* 2002a; 160: 251-8.

Stockfleth E, Meyer T, Benninghoff B, Salasche S, Papadopoulos L, Ulrich C, Christophers E. A randomized, double-blind, vehicle-controlled study to assess 5% imiquimod cream for the treatment of multiple actinic keratoses. *Arch Dermatol* 2002b; 138: 1498-1502.

Stockfleth E, Nindl I, Sterry W, Ulrich C, Schmook T, Meyer T. Human papillomaviruses in transplant-associated skin cancers. *Dermatol Surg* 2004a; 30: 604-609.

Stockfleth E, Christophers E, Benninghoff B, Sterry W. Low incidence of new actinic keratoses after topical 5% imiquimod cream treatment: a long-term follow-up study. *Arch Dermatol* 2004b; 140: 1542.

Stockfleth E, Sterry W, Carey-Yard M and Bichel J. Multicentre, open-label study using imiquimod 5% cream in one or two 4-week courses of treatment for multiple actinic keratoses on the head *British Journal of Dermatology* 2007, 157 (Suppl. 2), 41–46

Swanson N, Abramovits W, Berman B, Kulp J, Rigel DS, Levy S. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: results of two placebo-controlled studies of daily

application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol*. 2010 Apr;62(4):582-90.

Szeimies RM, Karrer S, Radakovic-Fijan S, Tanew A, Calzavara-Pinton PG, Zane C, Sidoroff A, Hempel M, Ulrich J, Proebstle T, Meffert H, Mulder M, Salomon D, Dittmar HC, Bauer JW, Kernland K, Braathen L. Photodynamic therapy using topical methyl 5-aminolevulinate compared with cryotherapy for actinic keratosis: a prospective, randomized study. *J Am Acad Dermatol* 2002; 47: 258-262.

Szeimies RM, Gerritsen MJ, Gupta G, Ortonne JP, Serresi S, Bichel J, Lee JH, Fox TL, Alomar A. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol*. 2004 Oct;51(4):547-55.

Szeimies RM, Karrer S, Sauerwald A, Landthaler M. Photodynamic therapy with topical application of 5-aminolevulinic acid in the treatment of actinic keratoses: an initial clinical study. *Dermatology*. 1996;192(3):246-51.

Szeimies RM, Bichel J, Ortonne JP, Stockfleth E, Lee J, Meng TC. A phase II dose-ranging study of topical resiquimod to treat actinic keratosis. *Br J Dermatol* 2008 Jul;159(1):205-10.

Tarstedt M, Rosdahl I, Berne B, Svanberg K, Wennberg AM. A randomized multicenter study to compare two treatment regimens of topical methyl aminolevulinate (Metvix)-PDT in actinic keratosis of the face and scalp. *Acta Derm Venereol* 2005;85:424-8

Thai KE, Ferguson P, Freeman M et al. (2004) A prospective study of the use of cryosurgery for the treatment of actinic keratoses. *Int J Dermatol* 43:687–692

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

Trakatelli M, Ulrich C, del Marmol V, Euvrard S, Stockfleth E, Abeni D. Epidemiology of nonmelanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. *Br J Dermatol*. 2007 May;156 Suppl 3:1-7.

Tschen EH, Wong DS, Pariser DM, Dunlap FE, Houlihan A, Ferdon MB; Phase IV ALA-PDT Actinic Keratosis Study Group. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol*. 2006 Dec;155(6):1262-9.

Tse Y, Ostad A, Lee HS et al. A clinical and histologic evaluation of two medium-depth peels. Glycolic acid vs. Jessner's trichloroacetic acid. *Dermatol Surg* 1996; 22:781-6.

Ulrich C, Christophers E, Sterry W, Meyer T, Stockfleth E. Skin diseases in organ transplant patients. *Hautarzt* 2002; 53: 524-533.

Ulrich C, Bichel J, Euvrard S, Guidi B, Proby CM, van de Kerkhof PCM, Amerio P, Rønnevig J, Slade HB, Stockfleth E. Topical immunomodulation under systemic immunosuppression: results of a multicentre, randomized, placebo-controlled safety and efficacy study of imiquimod 5% cream for the treatment of actinic keratoses in kidney, heart, and liver transplant patients. *Br J Dermatol*. 2007a, 157 (Suppl. 2), 25-31

Ulrich C, Hackethal M, Ulrich M, Howorka A, Forschner T, Sterry W, Stockfleth E. Treatment of multiple actinic keratoses with topical diclofenac 3% gel in organ transplant recipients: a series of six cases. *Br J Dermatol*. 2007b May;156 Suppl 3:40-2

Ulrich C, Degen A, Patel MJ, Stockfleth E. Sunscreens in organ transplant patients. *Nephrol Dial Transplant*. 2008 Jun;23(6):1805-8.

Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients - Where do we stand today? *Am J Transplant* 2008b.

Ulrich C, Jürgensen JS, Degen A, Hackethal M, Ulrich M, Patel MJ, Eberle J, Terhorst D, Sterry W, Stockfleth E. Prevention of non-melanoma skin cancer in organ transplant patients by regular use of a sunscreen: a 24 months, prospective, case-control study. *Br J Dermatol*. 2009;161 Suppl 3:78-84.

Ulrich C, Johannsen A, Röwert-Huber J, Ulrich M, Sterry W, Stockfleth E  
Results of a randomized, placebo-controlled safety and efficacy study of topical diclofenac 3% gel in organ transplant patients with multiple actinic keratoses. *Eur J Dermatol* 2010; 20:482-8

Ulrich M, Maltusch A, Röwert-Huber J, González S, Sterry W, Stockfleth E, Astner S. Actinic keratoses: non-invasive diagnosis for field cancerisation. *Br J Dermatol*. 2007;156 Suppl 3:13-7.

Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. *Inflamm res* 1995; 44:1-10; Wang D, DuBois RN. Prostaglandins and cancer. *Gut* 2006; 55:115-22.

Warino L, Tusa M, Camacho F, Teuschler H, Fleischer AB Jr, Feldman SR. Frequency and cost of actinic keratosis treatment. *Dermatol Surg*. 2006;32(8):1045-9.

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

Winton GB, Salasche SJ. Dermabrasion of the scalp as a treatment for actinic damage. *J Am Acad Dermatol* 1986; 14:661-8.

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

Wollina U, Konrad H, Karamfilov T. Treatment of common warts and actinic keratoses by Er:YAG laser. *J Cutan Laser Ther* 2001; 3: 63-6.

Wolf JR, Taylor JR, Tschien E. Topical 3% diclofenac in 2% hyaluronan gel in the treatment of actinic keratoses. *Int J Dermatol* 2001; 40:709-13.

Wulf HC, Pavel S, Stender I, Bakker-Wensveen CA. Topical photodynamic therapy for prevention of new skin lesions in renal transplant recipients. *Acta Derm Venereol*. 2006;86:25-8

Yu TC, Rahman Z, Ross BS. Actinic keratoses--surgical and physical therapeutic modalities. *Cutis* 2003; 71: 381-4.

Zouboulis ChC. Principles of cutaneous cryosurgery: An update. *Dermatology* 1999; 198: 111-117.

Zouboulis CC, Röhrs H. Cryosurgical treatment of actinic keratoses and evidence-based review Hautarzt. 2005 Apr;56(4):353-8.

## **9 Attachment - Strength of recommendations and quality of evidence (de Berker et al., 2007)**

### **Strength of recommendations**

- A There is good evidence to support the use of the procedure
- B There is fair evidence to support the use of the procedure
- C There is poor evidence to support the use of the procedure
- D There is fair evidence to support the rejection of the use of the procedure
- E There is no evidence to support the rejection of the use of the procedure

### **Quality of evidence**

- I Evidence obtained from at least one properly designed, randomized controlled trial
- II-i Evidence obtained from well-designed controlled trials without randomization
- II-ii Evidence obtained from well-designed cohort or case–control analytical studies, preferably from more than one centre or research group
- II-iii Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
- III Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees
- IV Evidence inadequate owing to problems of methodology (e.g. sample size, or length of comprehensiveness of follow up, or conflicts in evidence)