Guideline

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S2k guideline: Diagnosis and management of cutaneous lupus erythematosus – Part 1: Classification, diagnosis, prevention, activity scores

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- German Society for Pediatric Rheumatology (Gesellschaft für Kinder- und Jugendrheumatologie e.V., GKJR)

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Introduction

Table 1 shows the terms and symbols used for the standardized representation of our recommendations.

Clinical introduction

Cutaneous lupus erythematosus (CLE) is a rare, inflammatory autoimmune skin disease with heterogeneous clinical appearance. Currently, there is no treatment specifically approved for this disease. Topical and systemic medications are used off label. The goal of this guideline is to provide consensus-based recommendations on the diagnostics and treatment of patients with CLE, siehe Kommentar in accordance with the existing German S1 guideline from 2009 [1] and with the European S2K guideline [2]. Diagnostik und Therapie des kutanen Lupus erythematodes, AWMF-Register-Nr.: 013-060, 2020, www.awmf.org

Classification, pathophysiology, and epidemiology

Classification

Lupus erythematosus (LE) is a heterogeneous, inflammatory autoimmune disease which can involve many organs with a variable course [3]. Systemic lupus erythematosus (SLE) must be differentiated from cutaneous lupus erythematosus (CLE).

This guideline only covers the disease of CLE, even though in the literature CLE may not always be differentiated from cutaneous lesions associated with SLE [4]. The classification of the various skin manifestations of CLE is originally based on the work of James N. Gilliam who differentiated between LE-specific and non-LE-specific cutaneous lesions according to histological criteria [5]. LE-specific cutaneous manifestations (cutaneous lupus erythematosus, CLE) are further differentiated based on clinical, histopathological, serological, and genetic findings. This was modified and presented in the "Düsseldorf Classification" in 2004 (Table 2) [6, 7]. Examples of non-LE-specific cutaneous lesions that may quite frequently be associated with SLE include vascular skin disorders (periungual teleangiactasia, livedo racemosa, thrombophlebitis, Raynaud phenomenon).

Tables 3 and 4 summarize the clinical appearance and special characteristics of the various forms of chronic CLE (CCLE) and the intermittend CLE (ICLE). The clinical signs

Table 1 Strengths of recommendation – wording, symbolism and interpretation (modified in accordance to Kaminski-Hartenthaler et al., 2014).

Strength of recommendation	Wording	Symbol
Strong recommendation *in favor* of an approach	recommended	↑↑
Weak recommendation *in favor* of an approach	suggested	↑
No recommendation as to approach	may be considered	o
Recommendation *against* an approach	not recommended	↓

Table 2 Duesseldorf Classification of lupus erythematosus, modified in accordance to [1, 6, 7].

Acute cutaneous lupus erythematosus (ACLE)
Subacute cutaneous lupus erythematosus (SCLE)
Chronic cutaneous lupus erythematosus (CCLE) – Discoid lupus erythematosus (DLE) – Chilblain lupus erythematosus (CHLE) – Lupus erythematosus profundus/panniculitis (LEP)
Intermittent cutaneous lupus erythematosus (ICLE) – Lupus erythematosus tumidus (LET)

Table 3 Chronic cutaneous lupus erythematosus (CCLE), according to [1].

Discoid lupus erythematosus (DLE)

Clinical appearance

- Localized type (ca. 80 %)
  - Face and capillitium
- Disseminated type (about 20 %, frequently associated with SLE)
  - Also upper trunk and extensor sides of limbs
- DLE of the oral mucous membranes
  - Buccal mucous membranes >> palate

Special characteristics

- Most common type of CCLE
- Discoid erythematous plaques with tightly adhering follicular hyperkeratoses and hyperesthesia
- Manual removal of keratosis ("carpet tack sign") is painful
- Active margin with erythema and hyperpigmentation
- Scarring with central atrophy and hypopigmentation, scarred alopecia in hirsute areas
- Discoid lesions in the lip area > buccal mucous membranes
- Mutilations in the area of nose and mouth, vermicular perioral scarring
- Provocation by irritant stimuli (Koebner's phenomenon) may occur

Continued

- In rare cases, squamous cell carcinoma may develop in healed scars
- ANA with high titers (rarely, in ca. 5 %), usually no anti-ds-DNA antibodies, rarely antibodies against Ro/SSA or U1-RNP
- In 10 % of cases, DLE is the first sign of SLE

Lupus erythematosus profundus (LEP; Synonym: LE panniculitis)

Clinical appearance and special characteristics

- Subcutaneous, nodular or discoid, firm infiltrations, with secondary adherence to the overlaying skin
- *Surface of the lesions:* inflammatory erythema, no alteration, or simultaneous DLE
- *Predilection sites:* Gluteal or hip area, thighs, upper arms, face, chest
- In rare cases, periorbital edema may occur as an initial sign
- Ulceration and calcification may occur
- Healing may result in scars and deep lipatrophy
- ANA positive in up to 75 %; usually no anti-ds-DNA antibodies, occurrence of anti-ds-DNA antibodies may signify transition into SLE
- ACR criteria from 1982 are formally fulfilled in 35–50 %, association with SLE is more rare

Chilblain lupus erythematosus (CHLE) Clinical appearance and special characteristics

- Livid swellings that are painful on pressure, as well as large, cushion-like nodes, partly with central erosion and ulceration
- *Predilection sites:* symmetrical acral areas exposed to the cold (dorsal and marginal regions of the fingers, tips of the toes, heels, ears, nose)
- EIGENER PUNKT*:* Occurrence in the cold and damp seasons or after a drop in temperature
- Clinical and histological differentiation from genuine chilblains (perniones) is difficult
- ANA, anti-Ro/SSA antibodies and positive rheumatoid factors are variable; usually no anti-ds-DNA antibodies
- Associated with SLE in about 20 %
- Familial "Chilblain lupus": First description of a monogenic, inherited form of CLE

and special characteristics of acute CLE (ACLE) and subacute CLE (SCLE) can be found in the supplement.

Pathophysiology

CLE is a cutaneous autoimmune disease with simultaneous activation of the innate and adaptive immune system [8, 9]. Depending on the patient's individual genetic disposition, and to some extent via immunostimulatory triggers (i.a. UV rays),

Table 4 Intermittent cutaneous lupus erythematosus (ICLE), according to [1].

Lupus erythematosus tumidus (LET)

Clinical appearance

- Succulent, indurated, urticaria-like erythematous plaques with smooth surface without involvement of the epidermis
- Lesions are often arranged in annular or sometimes semicircular patterns
- *Predilection sites:* areas exposed to light (especially face, upper trunk, cleavage, extensor sides of the arms)
- Healing without scars or pigment disorders

Special characteristics

- Pronounced photosensitivity (in > 70 % positive photoprovocation test with UVA and/or UVB)
- ANA in 10–30 % positive, anti-Ro/SSA and anti-La/SSB antibodies in about 5 %
- Varying course with very good prognosis, spontaneous remission may occur

an autoimmune response against the own epidermis occurs [10–12]. The histological correlation of this specific anti-epidermal inflammation is the so-called interface dermatitis. This is characterized by infiltration of the basal epidermal layer with cytotoxic lymphocytes and plasmacytoid dendritic cells (pDC), but also cell death of local keratinocytes. Based on the CLE subtype and the individual patient, different effector mechanisms of the immune system are involved. These include the adaptive immune response (mainly auto antibodies, T cells) as well as the innate immune response with activation of cell death, cytokine, and DAMP (damage-associated molecular pattern) pathways. Central pro-inflammatory factors include type I/III interferons and associated cytokines (mainly CXCL10) which are expressed both by pDC and keratinocytes, and are required for the recruitment of $CXCR3^+$ effector cells [13]. A key to understanding the development of skin lesions in CLE is that factors from the adaptive immune system (which is actually downstream) can trigger pathways of the (primary) innate immune system, resulting in a "permanently activated short circuit" [14].

Epidemiology

Due to the various subtypes, there is only a limited amount of valid data on the prevalence of CLE. Transition from CLE to SLE has been reported for 20 % of CLE patients within three to five years [15–18]. Up to 30 % of all CLE patients develop more than one subtype [17, 18]. CLE usually appears during the third to fourth decade of life, and the females to males gender ratio is much lower than with SLE (3 : 1 to 3 : 2) (9 : 1) [19, 20].

In three quarters of all patients with SLE, skin lesions develop during the course of the disease, and in one quarter the skin is even the initial manifestation. A Swedish publication puts the incidence of CLE at 4.0 per 100,000 [21]. Within the subtype of CCLE, discoid lupus erythematosus (DLE) is the most common form at 80 % [21]. DLE is most common in African Americans, while SCLE occurs predominantly in light-skinned European ethnicities. Chilblain LE (CHLE) and LE tumidus (LET) are found mostly in Europe [22–25].

Diagnostics

Diagnostics

Diagnostics of CLE should be based on the clinical and histological findings. Patients with CLE without systemic involvement often lack detectable autoantibodies, but if present the autoanti-bodies may help to support the diagnosis and to better assess the prognosis [4].

Histology

If CLE is suspected, the diagnosis should always be confirmed via skin biopsy (except in cases of ACLE if SLE has already been confirmed). Ideally, the specimen should be obtained from an active, non-treated lesion. Active lesions typically show interface dermatitis with anti-epidermal lymphocytic infiltration, vacuolization of basal keratinocytes, and colloid bodies [26, 27]. Acanthosis, dermal infiltrations, and mucin deposits may vary depending on the CLE subtype (Table 5).

Table 5 Prominent histological and immunohistological characteristics of lesions from cutaneous lupus erythematosus (CLE), modified in accordance to [11].

Subtypes	Histology/Immunohistology
CLE	▸ Interface dermatitis ▸ Hydropic degeneration of the basal epidermis ▸ Lymphoid infiltration (mostly plasmacytoid dendritic cells and T cells) ▸ Dermal mucin deposits ▸ Strong expression of chemokines regulated by interferons (MxA, CXCL10)
ACLE	▸ Discrete infiltrations with moderate interface dermatitis ▸ Sporadic neutrophils in the infiltrations as well as nuclear detritus
SCLE	▸ Interface dermatitis with few cells and cutaneous, perivascular infiltrations ▸ Moderate mucin deposits

Special stains

Special stains may help to confirm the diagnosis of CLE but are not obligatory. Some examples are alcian blue stains (dermal mucin deposits), PAS stains (basal laminae) [27], and detection of plasmacytoid dendritic cells (BDCA2, CD123) [28]. Surrogate markers of IFN activation (MxA) can visualize activation of the innate immune system within the lesion, which is characteristic for CLE [29].

Direct immunofluorescence

Direct immunofluorescence (DIF) can show lesional granular deposits of C3 as well as IgG and IgM in CLE. In uncertain cases, this test can help confirm the diagnosis of LE [26, 27, 30]. It should be noted that false-positive results may occur in skin areas exposed to light, especially in rosacea [31]. Non-lesional skin not exposed to light may show a higher number of positive DIF in SLE patients (lupus band) [30, 32]. However, the authors would like to stress that this test is insufficient to confirm the diagnosis of SLE, which must always be correlated with the clinical findings.

Recommendation	Strength	Agreement
A lesional biopsy is recommended for histological confirmation of a clinical of CLE diagnosis. Exceptions can be made in cases of 'butterfly rash' and/or mucosal lesions.	↑↑	100 %
Special stains as well as immunohistology are suggested to confirm diagnosis (examples include PAS, alcian blue, CD123, MxA).	↑	100 %
Direct immunofluoresence (DIF) is suggested in cases where differential diagnosis is difficult. Analysis of lesions not exposed to light is recommended.	↑ ↑↑	100 %
Direct immunofluoresence (DIF) of non-lesional skin exposed to light is not recommended.	↓	100 %

Photoprovocation

Photoprovocation with UV light according to a standard protocol is appropriate for confirming the diagnosis of photosensitive CLE subtypes [33]. After UV exposure, specific

CLE lesions will only appear after a latency of 8 ± 4.6 days and will then persist for a considerable time. In contrast, other photodermatoses such as polymorphous light eruption (PLE) will appear much earlier after UV exposure and the lesions will subsequently resolve. In addition to the clinical evaluation, UV-induced CLE lesions can be confirmed via biopsy [33].

Recommendation	Strength	Agreement
In special cases, standardized photoprovocation performed by experienced investigators is suggested (for example to exclude CLE, or to differentiate between CLE and polymorphous light eruption).	↑	100 %

Classification criteria of SLE

A working group from the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) has developed a scoring system for classification of SLE [34, 35] (Table 6). This has replaced the former ACR criteria (established in 1982, revised in 1997) and the SCLICC criteria (Systemic Lupus Erythematosus Collaborating Clinics Group, established in 2012) [34]. These two scores put equal emphasis on serological and clinical criteria. So far, four out of eleven criteria ACR criteria from 1982 contained mucocutaneous manifestations (butterfly rash, discoid lesions, light sensitivity, and oral ulcerations). Light sensitivity, in particular, can easily be interpreted differently, resulting almost certainly in over-estimation of SLE prevalence [4]. It has been shown that about 50 % of SLE patients, 10 % of DLE patients, and practically all ACLE patients will fulfill the criteria for SLE without necessarily having systemic (organ) involvement. The new criteria are designed for better differentiation between CLE and SLE [35].

Table 6 New EULAR/ACR SLE classification criteria, according to [35].

Prerequisite	ANA (HEp2-IFT) ≥ 1 : 80 (may vary depending on the normal range of the local laboratory)	
Basic conditions	– If other causes are present, such as infection, neoplasia, medications, or other diseases, a criterion is not counted. – At least one criterion needs to be currently present. – Criteria are fulfilled if they have been present (documented) at any time. – Criteria do not have to be present simultaneously. – Within each domain, only the highest score is counted for the total score.	
Clinical domains and criteria	**Weighting**	
Constitutional	Fever	2
Skin	Non-scarring alopecia	2
	Oral ulcers	2
	SCLE or DLE	4
	ACLE	6
Arthritis	Synovitis in ≥ 2 joints or pain on pressure in ≥ 2 joints with morning stiffness ≥ 30 minutes	6
Neurology	Delirium	2
	Psychosis	3
	Seizures	5
Serositis	Pleural or pericardial effusion	5
	Acute pericarditis	6
Hematology	Leukopenia	3
	Thrombocytopenia	4
	Autoimmune hemolysis	4
Kidneys	Proteinuria > 0.5 g/24 h	4
	Lupus nephritis (histol.) Type II, V	8
	Lupus nephritis (histol.) Type III, IV	10
Immunological criteria	**Weighting**	
Antiphospholipid AB	aCL>40 GPL or aß2G-PI>40 GPL or LA +	2
Complement	Low C3 or C4	3
	Low C3 *and* C4	4
Highly specific autoantibodies	Anti-ds-DNA AB	6
	Anti-Sm AB	
Classification SLE classification: ≥ 10 points		
EULAR/ACR criteria: sensitivity 98 %, specificity 97 %		

Recommendation	Strength	Agreement
Diagnosis: The use of the 2019 EULAR/ACR criteria is recommended in order to differentiate CLE from (Table 6).	↑↑	100 %
Monitoring: For any CLE patient, a reassessment of the 2019 EULAR/ACR criteria is suggested either once a year and/or in case of clinical/laboratory changes.	↑	100 %

Laboratory parameters

In patients with ACLE (which is most frequently associated with SLE) and/or in patients with SCLE (frequently associated with arthritis or other moderate organ involvement), laboratory investigations should always be performed to exclude or confirm organ involvement. Laboratory investigations are, however, not only useful in initial diagnostics but also for evaluation of prognosis and activity. In addition, drug side effects need to be monitored. We cannot give evidence-based recommendations for the frequency of laboratory investigations – this depends on individual factors such as severity and activity of the (cutaneous) disease, treatment, comorbidities and their treatment, as well as previous findings (such as detection of ANA or ENA) and changes in laboratory values (such as anti-ds-DNA antibodies or complement). Table 7 offers a list of recommended blood analyses in patients with CLE, including their significance.

Recommendation	Strength	Agreement
In CLE patients, it is recommended to analyse the blood and urine parameters listed in Table 6 for diagnosis as well as monitoring of disease activity and toxic drug side effects.	↑↑	100 %

Table 7 Recommended blood tests for patients with CLE and their relevance.

Test	Remarks
Blood count including differential blood count	Hematological disorders (anemia, leukopenia or lymphopenia as well as thrombocytopenia) are part of the SLE criteria but have also been reported to occur in CLE patients (anemia: 2–27 %; leukopenia: 0–30 %; thrombocytopenia: 2–4 % of patients). Abnormal values (mostly low cell counts) may either be an expression of disease activity or a toxic side effect of drug treatment.
ESR and CRP	ESR is typically increased in SLE patients (due to hypergammaglobulinemia, among other reasons) but may also be increased in 20–50 % of CLE patients. CRP increase in CLE/SLE usually indicates infection but may also be a sign of serositis or arthritis. If it can be explained by activity (for example arthritis) it is suitable for monitoring.
Creatinine and eGFR	Serum creatinine offers very low sensitivity in the early stages of lupus nephritis. Increases are frequently found only once renal function is severely impaired (blind area). Levels also depend on the patient's age and (among other things) muscle mass. Estimated glomerular filtration rates (eGFR) according to a standardized formula, or (rarely nowadays) creatinine clearance from a 24-hour urine collection are therefore more reliable. Elevated or increasing creatinine levels necessitate early consultation of a specialist for internal medicine/nephrology.
Urinalysis, urine sediment, and proteinuria	Urinalysis is required to screen for renal involvement. In case of abnormal values, urinalysis should be repeated and the urine sediment investigated. The protein (or albumin) to creatinine ratio in morning urine can be used for screening or monitoring of proteinuria. 24-hour urine collection for analysis is usually unnecessary. Reproducible abnormalities in urinalysis (for example erythrocyturia or proteinuria) necessitate consultation of a specialist for internal medicine/nephrology!

Continued

Table 7 Continued.

Test	Remarks
Hepatic function: ASAT, ALAT, γGT and ALP, bilirubin if indicated	Involvement of the liver in the sense of an overlap syndrome with autoimmune hepatitis (AIH) is rare in patients with CLE/SLE. Increased hepatic enzymes thus usually result from toxic side effects induced by medications (*drug-induced liver injury* [DILI]). Hepatic function should be monitored before and during medical treatment. Early consultation of internal medicine specialists and investigation of increased values (for example due to infection) is recommended.
CK and LDH	Increased CK may (rarely) result from myositis associated with SLE. In very rare cases, hydroxychloroquine treatment may cause myopathy with increase of CK. LDH may result from hemolysis; this can be investigated by determining haptoglobin.
Electrophoresis	Electropheoresis may detect alterations of serum proteins: Albumin is decreased in patients with lupus nephritis, 2–4 % of patients have monoclonal gammopathy (usually MGUS). Initial investigation to exclude other disorders (monoclonal gammopathies, IgA deficiency, hyper-IgE syndrome).
Antinuclear antibodies (ANA) (HEp-2 cell test)	ANA determination is *the* classic screening test for connective tissue diseases and should be performed in all patients with CLE. If present, ANA usually show low titers in CLE (≤ 1 : 320, *note*: this may vary between laboratories). Positive ANA is an obligatory criterion when diagnosing SLE (Table 6). Nowadays, ANA are described by their fluorescence according to the AC nomenclature [36]. Positive ANA should be further specified via ENA. The frequency of ANA and ENA varies depending on the clinical CLE subtype. Anti-Ro/SS-A antibodies (and less pronounced anti-La/SS-B), for example, are typical for SCLE. Anti-histone antibodies are frequently found in drug-induced LE while antibodies against ds-DNA and/or Sm are frequently detected in SLE (they are included in the new SLE criteria) but are not typical for CLE. Anti-ds-DNA antibodies can be used for monitoring disease courses and activity.
Antiphospholipid AB (APS-AB) and lupus anticoagulant	Antiphospholipid antibodies (APS-AB, most frequently cardiolipin, beta-2 glycoprotein, and the lupus anticoagulant) are included in the EULAR and ACR/SLICC criteria for SLE. They are serological markers for the antiphospholipid antibody syndrome (APS). APS antibodies are found in various CLE subtypes with large variations in frequency (5.8–68 %). Detection of (significant) APS-AB levels indicates SLE rather than CLE.
Complement C_3 and C_4	C_3 and/ or C_4 are included in the EULAR and ACR/SLICC criteria for SLE. Low levels of C_3 and/or C_4 are very typical for SLE while the levels are usually normal in CLE. If low levels are present, C_3 and C_4 are particularly well suited for monitoring disease course and activity. High levels of C_3 or C_4 can for example be found in infection (acute phase protein). In CLE patients, CH_{50}, C1q, and anti-C1q antibodies should only be determined if there is a strong suspicion of transition into SLE.

Organ-specific diagnostics and interdisciplinary investigations

In case of abnormalities in the laboratory or urinalysis investigations, further diagnostic steps such as X-rays, MRI, echocardiography, or ultrasound must be initiated. The musculoskeletal, hematological, renal, cardiopulmonary, and neurological systems need to be monitored. Studies have shown that 10–15 % of CLE patients developed systemic organ involvement within eight years. Case reports have also described CLE as a paraneoplastic disease; this applies almost exclusively to SCLE [1, 37, 38]. Appropriate screening investigations should be recommended to the patient, and their primary care physician informed.

In SLE patients, cardiovascular risk (hypertension, hyperlipidemia) is increased [39] due to various risk factors, both disease-specific (lupus nephritis, permanent disease activity, corticosteroids) and non-specific. Thus, appropriate screening should be performed.

Recommendation	Strength	Agreement
Based on clinical and/or laboratory findings, organ-specific diagnostics or referral to an appropriate specialist is recommended.	↑↑	100 %

Recommendation	Strength	Agreement
Monitoring of cardiovascular risk factors is recommended as part of basic diagnostics.	↑↑	90.1 %
Participation in the generally recommended cancer screening examinations (skin, colon, gynecology, prostate) is recommended for CLE patients.	↑↑	100 %

Differential diagnoses

Depending on the CLE subtype, various differential diagnoses need to be considered (summary in Table 8). Polymorphic light eruption (solar rash) is an important differential diagnosis; however, this has also been found to be frequently associated with SCLE or DLE before or after diagnosis [40].

Table 8 Differential diagnosis for cutaneous lupus erythematosus, in accordance to [1].

Subtype	Differential diagnoses
ACLE	
– localized	Dermatomyositis, rosacea, seborrheic eczema, tinea faciei (facial ringworm), erysipelas, perioral dermatitis
– generalized	Viral or drug-induced exanthema, erythema multiforme, toxic epidermal necrolysis
SCLE	Tinea corporis, psoriasis vulgaris, mycosis fungoides, erythema multiforme/toxic epidermal necrolysis, erythema annulare centrifugum (EAC), erythema gyratum repens, drug rash, nummular eczema, seborrheic eczema
DLE	Tinea faciei, actinic keratosis, lupus vulgaris, sarcoidosis
LEP	Various forms of panniculitis, subcutaneous sarcoidosis, polyarteritis nodosa, malignant lymphoma (especially subcutaneous panniculitis-like T-cell lymphoma), morphea profunda, subcutaneous granuloma annulare
CHLE	Perniones (chilblains), lupus pernio (chronic form of skin sarcoidosis on the acra), acral vasculitis/vasculopathy
LET	Jessner lymphocytic infiltration (JLIS)/palpable migratory arciform erythema, polymorphic light eruption, pseudolymhoma, B-cell lymphoma, plaque-like cutaneous mucinosis, solar urticaria

Prevention

Sun protection

CLE patients who show induction or exacerbation on exposure to UV radiation are very sensitive to light. Consistent sun protection is therefore an important preventive strategy [41, 42]. Sun exposure should be avoided especially around noon (11 am to 3 pm), and artificial UV radiation (such as tanning beds) is not recommended. Patients should be warned that clear glass (including car windows) does not protect against UV-A radiation [43, 44].

Apart from sun-protective clothing and broad-brimmed hats, sunscreen with chemical and/or mineral UV-A and UV-B filters is essential. This should be applied in sufficient quantity (about 2 mg/cm²) 20–30 minutes before sun exposure [45, 46]. A double-blind, intra-individual comparison study in eleven CLE patients who had developed specific lesions on photoprovocation found that one of the three test preparations (with Mexoryl SX/XL, among other ingredients) was able to prevent induction of skin lesions in 100 % of cases [47]. A retrospective analysis using the same sunscreen confirmed these results in 96 % of patients (47 CLE, 4 SLE) [48]. Another prospective, randomized, double-blind, intra-individual, vehicle-controlled study showed prevention of CLE during photoprovocation in 16 patients after application of a broad-band chemical and mineral UV-A/UV-B filter with added vitamin E as an antioxidant [33]. The sunscreens used in the abovementioned studies contained additional titanium dioxide as a mineral sunscreen. For CLE as well as other severe photodermatoses, sunscreens are not reimbursed by health insurance companies although this preventative strategy may reduce the need for topical and systemic medications [49, 50].

Recommendation	Strength	Agreement
Apart from sun protective clothing, consistent use of sunscreen in exposed areas is recommended at all stages of the disease, irrespective of the extent and the topical or systemic medication used.	↑↑	100 %

There are currently no approved medications for treating CLE, either topical or systemic. Treatment is based on a small number of randomized controlled trials. There are, however, consensus-based European recommendations for the treatment of CLE patients [2] which are reflected in an algorithm [2, 51]. This algorithm contains first-line, second-line, and third-line treatments. It has

been modified in the development of this guideline. Mepacrine is frequently not reimbursed by health insurance and is thus only mentioned as a possible addition in the first-line treatment.

Use of activity scores

CLASI/RCLASI

Several methods have been developed to assess disease activity in SLE, including ECLAM (*European Consensus lupus Activity Measurement*), BILAG (*British Isles lupus Assessment Group*), SLAM (*Systemic lupus Activity Measure*), or SELENA-SLEDAI (*Systemic lupus Erythematosus Disease Activity Index*). These scores encompass a broad spectrum of potential organ involvement in SLE (including skin involvement) but are not suited for precisely assessing the spectrum of cutaneous symptoms in CLE or SLE. In 2005, a validated clinical score for assessing activity and intensity of CLE was introduced (*Cutaneous lupus Erythematosus Disease Area and Severity Index* [CLASI]). The CLASI can be used to evaluate disease severity: Mild disease = CLASI activity 0–9, moderate disease: 10–20, severe disease: 21–70. CLASI reduction by four points or 20 % may be regarded as a therapeutic response. A revised form of the CLASI (RCLASI) includes additional clinical criteria, such as edema/infiltration or subcutaneous nodes/plaques, for the various forms of CLE. Validity and practicability of the RCLASI have been confirmed in a reliability analysis. Apart from evaluating therapeutic response and monitoring treatment, this score is also useful in diagnosing the various CLE subtypes [16, 52–59].

Recommendation	Strength	Agreement
Diagnosis: Use of CLASI or RCLASI is suggested for evaluating disease activity and intensity in CLE (see background information).	↑	100 %
Monitoring: Use of CLASI or RCLASI is suggested for monitoring therapeutic response.	↑	100 %

Quality of life

Skin manifestations in CLE may result in severe distress, such as disfiguring, scarring, painful CLE lesions, mucous membranes lesions, or alopecia. This in turn reduces patients' quality of life. There is currently no disease-specific method for evaluating quality of life in CLE patients. However, the use of general dermatological quality of life scores can be recommended, such as the DLQI (Dermatology Life Quality Index) or the Skindex-29. Treatment monitoring should always take into account that cosmetic aspects may strongly influence quality of life, in particular as regards scarring lesions on the face and scalp.

Recommendation	Strength	Agreement
Diagnosis and monitoring: Use of the DLQI or Skindex-29 (skin-specific methods for evaluating quality of life) is suggested for evaluating quality of life in CLE patients.	↑	100 %

Prognosis

CLE subtypes may, with varying frequency, lead to systemic organ involvement and thus transition into SLE [59]. A study with 28 male and 11 female patients showed that disseminated skin lesions in DLE are significantly more common in males than in females [58]. While transition into SLE is seen in < 5 % of cases in DLE, the most common subtype of CCLE, SCLE will lead to systemic organ involvement in about 10–15 % of cases, mostly with mild symptoms. If minimal symptoms are included, the proportion of patients with extracutaneous involvement is 14–27 % in DLE and 60–70 % in SCLE. The most common symptoms are arthralgia/arthritis, and proteinuria [59]. In SCLE, acral vasculitis is frequently associated with joint involvement [60]. Patients with disseminated DLE show more frequent extracutaneous involvement and thus have a higher risk of transition into SLE than patients with localized DLE on the face and scalp [61]. A prospective multicenter study confirmed these findings in 296 LE patients (245 DLE/SCLE, 51 SLE) [23].

Extensive skin lesions in CLE may be considered as a prognostic marker for the further course of the disease. Disseminated DLE carries a higher risk of transition into SLE than localized DLE. Significantly increased ANA titers, antibodies against extractable nuclear antigens (ENA) such as anti-Sm antibodies, newly emerging anti-ds-DNA antibodies, increased ESR, proteinuria, hematuria, and arthritis are considered indicative for transition into SLE, particularly if they occur simultaneously [62].

Conflict of interest

Please refer to the long version of this guideline at www.awmf.org.

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