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GUIDELINE

S2k guideline: Diagnosis and therapy of localized scleroderma

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Scleroderma Support Group

Summary

The updated S2k guideline deals with the diagnosis and therapy of localized scleroderma (LoS). LoS represents a spectrum of sclerotic skin diseases in which, depending on the subtype and localisation, structures such as adipose tissue, muscles, joints, and bones may also be affected. Involvement of internal organs or progression to systemic sclerosis does not occur. LoS can be classified into four main forms: limited, generalized, linear, and mixed forms, with some additional subtypes. For cases of limited skin involvement, the guideline primarily recommends therapy with topical corticosteroids. UV therapy can also be recommended. In subtypes with severe skin or musculoskeletal involvement, systemic therapy with methotrexate is recommended. During the active phase of the disease, systemic glucocorticosteroids can be used additionally. In cases of methotrexate and steroid refractory courses, contraindications, or intolerance, mycophenolate mofetil, mycophenolic acid, or abatacept can be considered as second-line systemic therapies. In the case of linear LoS, autologous adipose-derived stem cell transplantation can also be performed for correcting soft tissue defects.

KEYWORDS
Localized scleroderma, morphea, sclerodermia circumscripta, scleroderma en coup de sabre

TABLE 1 Strengths of recommendation – wording, symbolism and interpretation (modified in accordance to Kaminski-Hartenthaler et al., 2014[2]).

Strength	Wording	Symbol	Implication
Strong recommendation for the use of an intervention	„we recommend …"	↑↑	We believe that all or almost all informed people would make this choice.
Weak recommendation for the use of an intervention	„we suggest …"	↑	We believe that most informed people would make this choice, but a substantial number would not.
No recommendation with respect to an intervention	„…may be considered…"	0	At the moment, a recommendation in favour of or against an intervention cannot be made due to certain reasons (for example no reliable evidenceavailable, conflicting outcomes)
Weak recommendation against the use of an intervention	„we suggest against…"	↓	We believe that most informed people would make a choice against this intervention, but a substantial number would not.
Strong recommendation against the use of an intervention	„we recommend against…"	↓↓	We believe that all or almost all informed people would make a choice against this intervention.

PRELIMINARY REMARKS

This guideline is an update. Some sections were adopted without modification from the previous version of the guideline from 2014.[1]

For further information, please refer to the long version of the guideline at www.awmf.org or the online appendix.

The terms and symbols presented in Table 1 were used for the standardized representation of the recommendations.

DEFINITION

Recommendation	Strength	Consensus strength
We recommend that diagnosis and therapy of LoS should take place in collaboration with experts in LoS, including dermatologists, pediatric dermatologists, pediatric rheumatologists, and/or rheumatologists.	↑↑	100% Strong consensus

Localized scleroderma (LoS), also known as "morphea", represents a spectrum of sclerotic skin disorders with potential involvement of adjacent structures such as subcutaneous fat, muscles, joints, and bones depending on the subtype and location. Unlike systemic sclerosis, LoS does not affect internal organs such as the heart, lungs, kidneys, or gastrointestinal tract, and it does not progress to systemic sclerosis.

EPIDEMIOLOGY AND CLASSIFICATION

Recommendation	Strength	Consensus strength
We *recommend* classifying LoS into four main types: limited, generalized, linear, or mixed. Additional subtypes may also exist (Table 2).	↑↑	100% Strong consensus

The incidence of LoS is reported to be approximately 27 per 1 million inhabitants.[3,4] In a survey conducted in England and Ireland, an incidence rate of juvenile LoS was described as 3.4 cases per 1 million children per year.[5] Localized scleroderma occurs more frequently in women than in men, with a ratio of 2.6–6 to 1.[3] The broad clinical spectrum of LoS has led to the development of various classifications.[6–8] For this guideline, a classification is proposed that takes into account the extent, spread, and depth of the fibrotic process. This results in a categorization into four main types: "limited, generalized, linear, and mixed" (Table 2). The advantage of this simple classification is its clear correlation with the therapeutic recommendations of this guideline.

This classification also partially reflects the distinct clinical course of each subgroup. For the limited variant, regression is reported in approximately 50% of patients

TABLE 2 Classification of localized scleroderma.

Limited type
- Morphea (plaque type)
- Guttate morphea (special type of morphea)
- Atrophodermia Pierini-Pasini (special type of morphea)
- Deep morphea

Generalized type
- Generalized localized scleroderma (involvement of at least three anatomical areas)
- Disabling pansclerotic morphea (severe variant)

Linear type
- Linear localized scleroderma (mostly affecting the extremities)
- Linear localized scleroderma, "en coup de sabre" type
- Progressive facial hemiatrophy (synonym: Parry-Romberg syndrome)
- Eosinophilic fasciitis (special type with predominant fascial involvement)[1]

Mixed type

Notes: The *limited* subtypes with exclusive cutaneous involvement include the plaque type (classic morphea), guttate morphea, and Atrophodermia Pierini-Pasini. Subtypes with extracutaneous involvement include deep morphea, linear localized scleroderma with subtypes *en coup de sabre* and progressive facial hemiatrophy, as well as eosinophilic fasciitis, and the generalized type with the subtype "disabling pansclerotic morphea".

[1] According to the authors, eosinophilic fasciitis is considered a special type of localized scleroderma, best classified under the linear types.

after approximately 2.5 years.[4,9] In contrast, the generalized and linear types are associated with a longer average duration of approximately 5.5 years. However, these are only average values, as secondary changes such as hyperpigmentation, depigmentation, contractures, and atrophic changes typically exhibit minimal and/or slow regression. The frequency patterns for the various subtypes are age-dependent, with the linear form being significantly more prevalent in childhood.[10] Especially in childhood, patients can be affected by multiple types, such as linear in combination with limited subtypes.

Limited type of localized scleroderma

The most common type of LoS is the plaque type (morphea). Characteristic predilection sites include the trunk, especially the submammary region, and the transition from the hip region to the inguinal region. The frequently oval lesions can appear erythematous in the early phases and then progressively become firm centrally, with a whitish or ivory-like color. Active lesions are characterized by a lilac-colored halo surrounding the fibrosing center, known as the "lilac ring". During the course of the disease, sclerotic lesions often become softer, sometimes atrophic, and may exhibit hypo- or hyperpigmentation. Depending on the location of fibrosis, the disease may also lead to the loss of hair and skin appendages in the affected area.

The guttate form of LoS (guttate morphea) is characterized by a trunk-dominant spread of yellowish-white, superficially shiny, sclerotic small lesions (<1 cm, with clinical activity demarcated by a "lilac ring"). Initially, these lesions may also present only as erythematous macules. Atrophodermia Pierini-Pasini may represent an early abortive form of the guttate form. The clinical picture of this form, which often manifests in childhood, is characterized by symmetrically occurring lesions on the trunk, smaller than 1 cm in diameter, sometimes erythematous, leading to a canoe-like depression below the skin level due to a loss of connective tissue. The histology corresponds to the late atrophic types of LoS.[11]

By far the rarest variant of the limited form of LoS is the deep form (less than 1% of cases). In this variant, the fibrotic process primarily develops in the deeper components of connective tissue, i.e., adipose tissue, fascia, or underlying muscle structures. The lesions typically manifest unilaterally or symmetrically, predominantly on the extremities. The deep form of LoS, also known as "deep morphea", can occur in childhood and, in some cases, may manifest without a preceding inflammatory reaction.

Generalized type of localized scleroderma

This form is present when at least three anatomical locations are affected. The most common locations include the trunk, thighs, and lumbosacral region. The plaques often appear symmetrically and can coalesce into larger areas. Frequently, the plaques occur in different stages of the disease.

A special, very rare variant of the generalized form of LoS is "disabling pansclerotic morphea". It is a rare and severe variant characterized by the combination of linear and disseminated LoS with extensive skin involvement and only a minimal tendency for regression of fibrosis. It entails the obligatory involvement of extracutaneous structures, often leading to severe contractures and complications in wound healing and sometimes extensive ulcers.

Linear type of localized scleroderma

Linear LoS is characterized by linear, band-like, or systematically occurring lesions. In milder types, these lesions may heal predominantly with hyperpigmentation or present as firm, sclerosing stripes extending over joints, leading to significant movement restrictions. Concurrently, underlying muscle or bone atrophy may be observed in the affected skin areas. The most known linear form is the so-called *en coup de sabre* type, which typically extends frontoparietally, usually paramedially from the eyebrows to the hairy scalp, resulting in scar-related alopecia. Often, there is involvement of the underlying central nervous system (CNS).

A condition closely related to linear LoS is progressive facial hemiatrophy (synonym: hemiatrophia faciei or Parry-Romberg syndrome [PRS]). This very rare condition is characterized by the primary atrophic transformation of the affected subcutaneous tissue, muscle, and bone, sometimes accompanied by hyperpigmentation of the overlying skin. Skin fibrosis is rare or absent. This condition often begins in adolescence and childhood in the head area (see section "special considerations in childhood") and progressively affects the cheek muscles, bones, and even the tongue.[12–14] This process may result in a pronounced asymmetry of the face. The simultaneous occurrence of linear LoS of the *en coup de sabre* type and progressive facial hemiatrophy is relatively common, with a reported coincidence of up to 40%.[15] Central nervous system involvement is not uncommon (see section "Radiological examinations"). Antinuclear antibodies are detected in up to 50% of patients in this subtype.

Eosinophilic fasciitis (Shulman syndrome) is considered by many experts as a distinct form of LoS and, in our opinion, can be most appropriately categorized within the spectrum of linear types. Clinically, it is characterized by progressive fibrosis of the proximal and/or distal extremities with variable skin retraction (negative venous sign [groove sign] and mattress phenomenon), caused by the deeper fibrotic process in the fascial and subcutaneous septa. The condition often occurs following trauma and is characterized in the early stages by blood and tissue eosinophilia.

TABLE 3 Basic and specialized laboratory in localized scleroderma.

Basic laboratory
- Complete blood count (especially important in linear types and eosinophilic fasciitis [eosinophilia])
  - Clinical chemistry
  - Transaminases (GOT, GPT)
  - Cholestasis parameter (γGT und AP)
  - Lactate dehydrogenase (LDH)
  - Creatinine
  - Creatine kinase (CK) (especially if concomitant myositis is suspected)
  - ESR and/or CRP
- Antinuclear antibodies (HEp-2 cells)

Further diagnostics: Screening for antibodies against extractable nuclear antigens only in case of suspicion of another autoimmune disease (anti-scl-70 or anti-centromere antibodies; anti-histone antibodies are often detectable in linear types of the extremities in childhood).
- Rheumatoid factors or CCP in case of arthritic complaints.

*Depending on the clinical presentation, not all laboratory parameters might be necessary for every patient.

Mixed type of localized scleroderma

In a small proportion of patients, cutaneous manifestations occur that can be classified into multiple subtypes of LoS. This is particularly evident in childhood LoS. Clinically, the most common presentation is a combination of linear form with either morphea (plaque type) or linear form together with a generalized form.

ASSOCIATION WITH OTHER AUTOIMMUNE DISEASES

The increased occurrence of other autoimmune diseases in LoS has been known for many years.[16] In a study published in 2009 involving 245 patients with LoS, 17.6% of cases (four times higher than in the general population) showed concurrent rheumatic or autoimmune diseases.[17] This was significantly more common in adults than in children. Patients with generalized LoS had a significantly higher prevalence (45.9%; twelve times higher than in the general population) of associated autoimmune diseases compared to patients with other types (9.6%). The most common associated autoimmune diseases included psoriasis, systemic lupus erythematosus, multiple sclerosis, and vitiligo. Overall, 16.3% had a positive family history of autoimmune diseases, with children (23.8%) being more affected than adults (10.6%). In a retrospective study of 472 LoS patients, 8.1% had associated autoimmune diseases such as Hashimoto's thyroiditis, rheumatoid arthritis, alopecia areata, and diabetes mellitus.[18]

The coexistence of LoS and lichen sclerosus has mainly been described in case reports and smaller case series with predominant overlaps involving extragenital lichen sclerosus.[19,20] In a prospective study from France published in 2012 involving 76 LoS patients, 38% also had genital lichen sclerosus, predominantly affecting patients with morphea (plaque type) and generalized LoS.[21] A subsequent retrospective study from Germany confirmed this high prevalence of genital lichen sclerosus in LoS.[18]

PATHOGENESIS

See long version of the guideline.

LABORATORY PARAMETERS

Recommendation	Strength	Consensus strength
We *recommend* a blood test for all types of LoS to determine basic laboratory values (complete blood count and clinical chemistry) and antinuclear antibodies (ANA) (see Table 3).	↑↑	100% Strong consensus
We *recommend* screening for extractable nuclear antigens (ENA) antibodies only in cases that are suspicious of another autoimmune disease.	↑↑	100% Strong consensus
We *recommend against* conducting Lyme disease diagnostics in cases of LoS without clinical indications of a Borrelia infection.	↓↓	100% Strong consensus
We *suggest* determining rheumatoid factor or CCP antibodies in case of arthritic symptoms.	↑	> 75% Consensus

An overview of the basic laboratory and specialized laboratory for localized scleroderma is shown in Table 3.

For further information, see longversion of the guideline.

HISTOLOGY

Recommendation	Strength	Consensus strength
We *recommend* performing a biopsy for histological confirmation of LoS diagnosis in cases of unclear clinical findings (standard fixation in formalin is sufficient).	↑↑	100% Strong consensus
If a biopsy is taken in cases of clinical suspicion of a deep, generalized, and/or linear form, *we recommend* an excisional biopsy involving the subcutaneous and adipose tissue due to the involvement of deeper structures.	↑↑	100% Strong consensus
If a biopsy is taken in cases of clinical suspicion of eosinophilic fasciitis, *we recommend* a deep excisional biopsy including the fascia.	↑↑	100% Strong consensus

For further information, see longversion of the guideline.

CLINICAL SCORES AND INSTRUMENTAL DIAGNOSTICS

Recommendation	Strength	Consensus strength
We recommend a MRI of the brain to exclude central nervous system involvement in cases of linear LoS of the *en coup de sabre* type and progressive facial hemiatrophy.	↑↑	100% Strong consensus

Recommendation	Strength	Consensus strength
We recommend using the validated LoSCAT for scientific studies to quantify disease activity and disease-related damage.	↑↑	> 50% Agreement of the majority

Recommendation	Strength	Consensus strength
As potential techniques for assessing the course of LoS, in addition to 20-MHz sonography, the computerized skin score, cutometer, durometer, thermography, and laser doppler measurements *may be considered*.	0	100% Strong consensus

Radiological examination

Due to the presence of neurological symptoms such as migraine, hemiparesis, and epilepsy observed in linear types of LoS, such as the subtype *en coup de sabre* and the closely related PRS, a neurological examination is recommended. Moreover, a MRI of the brain is recommended to rule out central nervous system involvement.[12,22–27] Subcortical calcifications and brain atrophy have been frequently described. Often, patients remain clinically asymptomatic despite the presence of central nervous system involvement. Nevertheless, they can also be the cause of the aforementioned neurological symptoms. Since children often may not provide clear information regarding potential neurological, arthralgic, and/or ocular complaints, the decision to use radiological follow-up examinations should be made collaboratively with treating physicians and parents.

Furthermore, MRI examinations are necessary for planning surgical interventions (for example in the subtype *en coup de sabre*) or for the clarification of musculoskeletal/ossary and subcutaneous manifestations, for example in the context of linear LoS.[12,24,27–29] Additionally, they are helpful for therapy monitoring.[30,31] In cases of deep LoS or eosinophilic fasciitis, where the activity in deeper tissues is often clinically challenging to assess, MRI is increasingly used.[31–33]

Interdisciplinary diagnostics

Potential ocular involvement should be evaluated by ophthalmologists, mucocutaneous involvement by dermatologists/dentists, temporomandibular joint involvement by orthodontists/rheumatologists, and neurological complaints by neurologists in patients with linear LoS (subtypes *en coup de sabre* and PRS).[27,34–38] Additionally, hip imbalance due to leg length discrepancy in linear LoS should be assessed and corrected by orthopedic specialists to prevent long-term damage.

For further information, see longversion of the guideline.

DIFFERENTIAL DIAGNOSIS – DISTINGUISHING FROM OTHER FIBROTIC DISEASES

Recommendation	Strength	Consensus strength
We recommend conducting a targeted medical history and physical examination for other autoimmune diseases and rheumatic conditions when LoS is present.	↑↑	100% Strong consensus
We recommend conducting further investigations if there are indications of autoimmune diseases and rheumatic conditions.	↑↑	100% Strong consensus
We recommend conducting a clinical examination of the anogenital region, especially in patients with morphea (plaque type) and generalized LoS, to screen for the presence of genital lichen sclerosus.	↑↑	100% Strong consensus

An overview of all relevant differential diagnoses is shown in Table 4.

For further information, see longversion of the guideline.

SPECIAL CONSIDERATIONS IN CHILDHOOD

While the limited type of LoS (morphea) primarily occurs in adults, linear types are more prevalent in childhood. Suspected "triggers" of onset include trauma, infections, genetic factors, and embryonic developmental disorders. Recent studies involving 65 children suggested that linear LoS appears to preferentially follow the lines of Blaschko, potentially indicating a mosaicism of embryonic cell associations.[39] In the largest study to date involving a total of 750 children, it was demonstrated that linear LoS on the extremities occurs most frequently at 65%, followed by the limited form (plaque type) at 26%, generalized form at 7%, and deep form at 2%. Twenty-three percent of patients had LoS in the head/face region (linear LoS of the *en coup*

TABLE 4 Differential diagnoses of localized scleroderma.

Early inflammatory phase of limited localized scleroderma (morphea)
• Lichen sclerosus
• Erythema chronicum migrans
• Cutaneous mastocytosis
• Granuloma annulare
• Radiation dermatitis
• Mycosis fungoides
• Drug reactions
Late stage of limited localized scleroderma (morphea) with predominant hyperpigmentation
• Postinflammatory hyperpigmentation
• Lichen planus actinicus
• Café au lait spots
• Erythema dyschromicum perstans
Late stage of limited localized scleroderma (morphea) with predominant atrophy
• Acrodermatitis chronica atrophicans
• Lipodystrophy
• Lichen sclerosus
• Scar
Late stage of limited localized scleroderma (morphea) with predominant sclerosis
• Necrobiosis lipoidica
• Pretibial myxedema
Generalized localized scleroderma
• Systemic sclerosis
• Pseudoscleroderma
• Scleroderma adultorum Buschke
• Scleromyxedema
• Sclerodermiform graft-versus-host disease
• Mixed connective tissue disease
• Nephrogenic systemic fibrosis
Linear localized scleroderma of the *en coup de sabre* type
• Panniculitides
• Progressive partial lipodystrophy
• Focal dermal hypoplasia
• Steroid atrophy
• Lupus erythematosus profundus

de sabre type and progressive facial hemiatrophy). In 12% of cases, there was a positive family history of rheumatic and autoimmune diseases.[10] Similar results were observed in an analysis including a total of 552 children with localized and systemic sclerosis.[40] Consequently, the linear type of LoS is clearly the most common form in childhood, with the coexistence of different subtypes not uncommonly found (see section epidemiology and classification).

Juvenile linear LoS on the extremities is generally characterized by a more severe course as compared to adults and can lead to significant skin and muscle atrophy, contractures, limb shortening, and reduced circumference. This often results in considerable functional to mutilating, cosmetic, and psychological limitations for affected patients. Osteoarticular complications such as arthralgia and arthritis of the affected limb are found in 30%–50% of patients.[41–43] The linear LoS of the *en coup de sabre* type and progressive facial hemiatrophy almost exclusively occurs in early childhood. It is likely one disease spectrum with partially overlapping features. In contrast to other subtypes of LoS, the course is slow and insidious, with the active phase of the disease usually lasting significantly longer (see section epidemiology and classification). Neurological symptoms are common and can manifest as epileptic seizures, neuropsychiatric symptoms, headaches, behavioral disorders, and learning difficulties.[13,44,45] Brain biopsies have revealed ipsilateral gliotic areas and perivascular inflammatory infiltrates.[46] Depending on the extent and severity, the involvement can also affect the cheek, nose, and upper lip, and other facial areas such as the chin region. Ophthalmological changes are diverse and can be associated with uveitis, eye muscle dysfunction, loss of eyebrows, or changes in the eyelids.[35]

"Disabling pansclerotic morphea", a very rare subtype of generalized LoS, typically manifests before the age of 14 and is characterized by a rapid disease progression with obligatory involvement of extracutaneous structures (subcutaneous fat, muscles, and bones). Severe growth retardation and even cachexia might occur.

The limited type (mostly plaque type), deep type (deep morphea), and eosinophilic fasciitis progress similarly to adults, and can also be associated with other types of LoS.

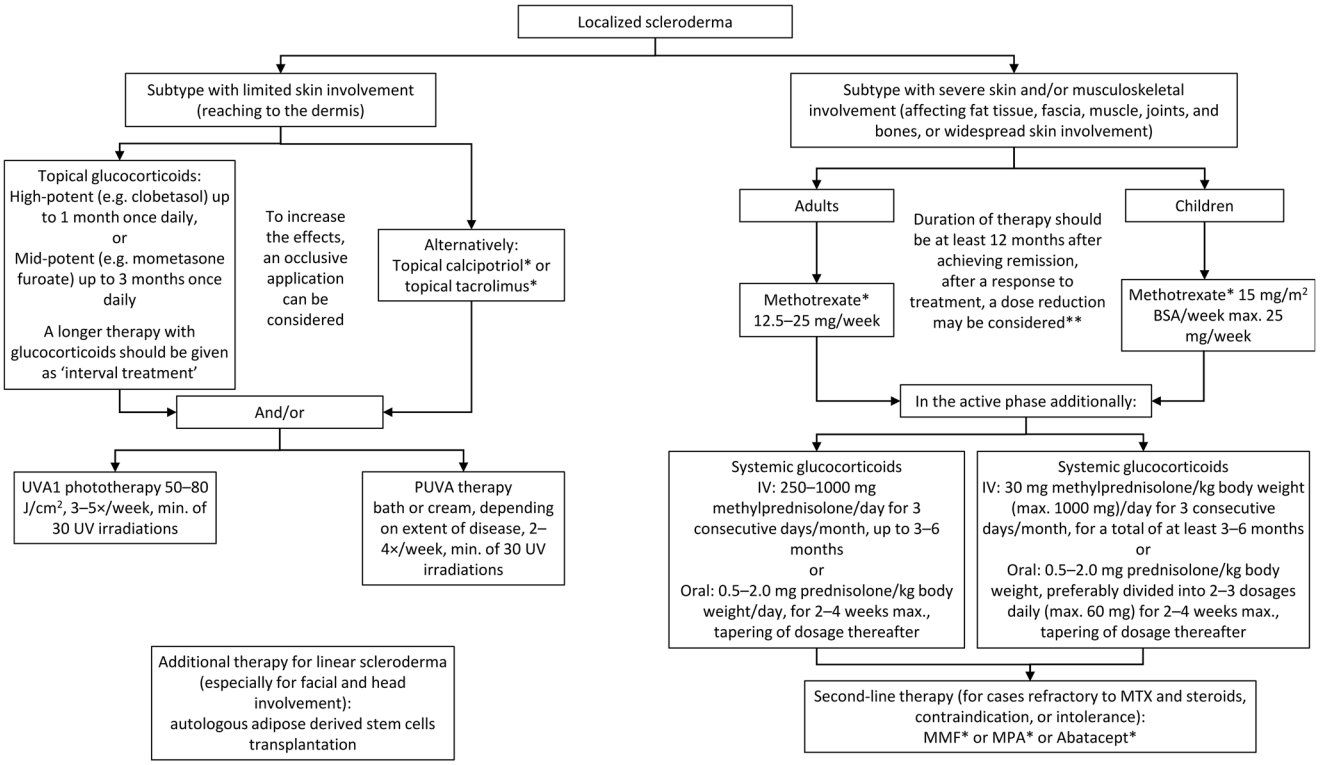
Special considerations in serology and diagnosis of localized scleroderma in childhood

As described in the "laboratory parameters" section, serological changes are often detectable in childhood LoS. In the generalized form, eosinophilia, typical of active eosinophilic fasciitis, may be present during the early, active stage. The most common laboratory abnormalities are observed in linear types. In the active phase of the disease, elevated rheumatoid factor, increased erythrocyte sedimentation rate, and hypergammaglobulinemia (elevated IgA and IgM during active disease and elevated IgG in severe disease with contractures) can occur. In linear LoS types, antinuclear antibodies often exhibit a homogeneous pattern. Elevated anti-histone and ssDNA antibodies may be detectable in extensive linear types with joint involvement.[47] Antibodies against extractable nuclear antigens are usually not detectable.

Since joint involvement is common in linear LoS of the extremities, a thorough examination of the joints, including the temporomandibular joint, should be conducted at both diagnosis and follow-up. Depending on the findings, further radiological diagnostics (ultrasound, magnetic resonance imaging, if necessary, X-ray) should be performed.[48]

Initial ophthalmological and, if necessary, ophthalmological follow-up examinations, including screening for uveitis, are recommended for patients with LoS, especially those with lesions on the face and scalp.

In cases of neurological/ophthalmological symptoms associated with LoS of the "en coup de sabre" type and progressive facial hemiatrophy, an MRI is recommended (see radiological examination section).



Adapted from the EDF guideline "European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin"

In cases of subtypes of linear scleroderma with involvement limited to the dermis that do not adequately respond to topical or phototherapy, systemic therapy may be considered.

MMF, Mycophenolate mofetil. MPA, Mycophenolic acid.
*, off-label treatment. **, see backgroundtext of treatment chapter

FIGURE 1 Treatment algorithm.

In a multinational study, organ involvement (lungs: 2.6%, heart: 1%, kidney: 1%) was reported in 750 patients with juvenile LoS.[10] The authors of this guideline have not observed the above-mentioned organ involvement in any case, so routine imaging work-up (as in systemic sclerosis) are not deemed necessary for juvenile LoS.

Special considerations in treatment of localized scleroderma in childhood

In the opinion of the authors, exclusive topical treatment may be appropriate for:

- Patients with small, localized, superficial, non-progressive LoS.
- Those not involving a joint.
- Lesions occurring in non-cosmetically sensitive areas.

However, in all other cases and for active linear LoS in childhood, potent systemic therapy should be initiated as early as possible to prevent potential late complications (contractures, growth disturbances, limb deformities, etc.). A longer duration until the start of therapy is associated with a higher frequency of treatment failure.[49] Treatment should be tailored according to the subtype and pattern of involvement, similar to adults (Figure 1). It is crucial to accompany this with physiotherapy (physical therapy, manual lymphatic drainage, see treatment section). Orthopedic interventions (for example surgical corrections like Achilles tendon lengthening or epiphysiodesis on the healthy leg to equalize leg length discrepancy) should only be performed in the long-standing inactive stage of the disease.[42] The same applies to cosmetic-aesthetic procedures in linear LoS of the *en coup de sabre* subtype and progressive facial hemiatrophy.

TREATMENT OF LOCALIZED SCLERODERMA

A causal therapy for LoS does not exist so far. However, effective treatment approaches are available, especially in the active phase of the disease. The proposed treatment algorithm considers the extent, severity of the disease, and the subtype (Figure 1). This is crucial since certain types of the limited type of LoS often cause no subjective complaints and only pose a "cosmetic" concern. On the other hand, some types of linear LoS can lead to severe and persistent physical and psychological impairment and should, therefore, be systemically treated in the early phase. After

inflammation subsides in these cases, systemic therapy should be continued for at least another 12 months. In case of clinical improvement, dose reduction may be considered. When assessing the effectiveness of the chosen therapeutic concept, it should be noted that the reduction of sclerosis typically takes at least 8 to 12 weeks in most cases.

Topical treatment

Recommendation	Strength	Consensus strength
We recommend topical treatment for LoS with limited skin involvement during the active phase using medium- to high-potency glucocorticosteroids (high potency for up to 4 weeks, medium potency for up to 12 weeks) once daily.	↑↑	100% Strong consensus
To enhance effectiveness, the application of glucocorticosteroids under occlusion *may be considered*.	0	100% Strong consensus
We recommend conducting a prolonged glucocorticosteroid therapy as interval treatment.	↑↑	100% Strong consensus

Recommendation	Strength	Consensus strength
We suggest using topical calcipotriol (off-label) as an alternative to topical monotherapy with glucocorticosteroids, either as a monotherapy or in combination with topical glucocorticosteroids for treating LoS.	↑	> 50% Agreement of the majority

Recommendation	Strength	Consensus strength
We suggest using topical tacrolimus (off-label) as an alternative to topical therapy with glucocorticosteroids for treating LoS.	↑	100% Strong consensus

Topical/intralesional application of glucocorticosteroids

Glucocorticosteroids are commonly used as the first choice for LoS among topical treatments in clinical practice. Similar to many other chronic inflammatory skin conditions, there are no studies on the efficacy of topical steroids in LoS. According to the authors' experience, topical corticosteroids are effective, especially in the active phase of superficially localized subtypes, such as morphea (plaque type). High-potency topical corticosteroids should be applied once daily for one month or medium-potency corticosteroids for three months. Occlusion therapy may be considered to enhance skin penetration. Prolonged corticosteroid therapy should be performed as interval therapy. Intralesional corticosteroid applications are only appropriate for the rare linear subtype *en coup de sabre* in the active border area. Triamcinolone acetonide, 10–40 mg pure or diluted 1:2–1:4 with lidocaine, is most commonly injected. However, there are no studies in the international literature on this frequently used treatment approach.

Topical calcipotriol

Apart from case reports, there are two therapeutic studies involving a total of 31 patients on the successful use of topical calcipotriol 0.005% in LoS.[50,51] In one study, calcipotriol 0.005% was combined with low-dose UVA1 phototherapy. Both studies used a twice-daily treatment regimen, with occlusive application of calcipotriol 0.005% in the monotherapy study. According to the authors, calcipotriol 0.005% is particularly suitable for superficial types of LoS, such as the plaque type, and can also be combined with topical glucocorticosteroids.

Topical calcineurin inhibitors

In contrast to topical glucocorticosteroids, there is a double-blind, randomized study on the use of tacrolimus 0.1% ointment in ten patients and an open-label study on tacrolimus 0.1% under occlusion in seven patients with LoS.[52,53] In the latter study, some clinical lesions were treated with vaseline as control lesions.[53] In another study involving 13 patients using tacrolimus 0.1% (with or without occlusion) and a long follow-up period of 4 years, nine patients showed a significant response.[54] Thus, all previous studies have shown a clear therapeutic success with tacrolimus. Due to its effectiveness in LoS, tacrolimus 0.1% can be considered as an alternative treatment to topical glucocorticosteroids in the active phase of the disease. Studies on the use of topical pimecrolimus have not been conducted in LoS to date, there are only case reports.[55]

For further information, see longversion of the guideline.

Phototherapy

Recommendation	Strength	Consensus strength
We recommend using medium-dose UVA1 phototherapy as the first-line phototherapy for limited subtypes of LoS.	↑↑	> 75% Consensus
We suggest using bath or cream PUVA therapy as an alternative phototherapy for LoS.[1] [1] does not apply to pediatric patients	↑	> 75% Consensus
Narrowband UVB phototherapy *may be considered* for LoS.	0	> 50% Agreement of the majority

Ultraviolet (UV) radiation therapy is one of the most effective treatment modalities for sclerotic skin conditions.[56–59] This is based on the observation that UVB can induce interstitial collagenase (matrix metalloproteinase-1) in vitro.[60] Building upon this insight, healthy skin was subsequently exposed to long-wave UVA light, demonstrating induction of interstitial collagenase in this context as well.[61] UV therapy exhibits both anti-inflammatory and anti-fibrotic effects. UV induces apoptosis of dermal T cells, depletion of Langerhans cells, and modulation of numerous pro-inflammatory cytokines.[58] The anti-fibrotic effect is realized, as described above, through the induction of various matrix metalloproteinases, leading to the inhibition of collagen production.[61–64] Additionally, there is a reduction in collagen cross-linkages, which are more prevalent in LoS, contributing to a decrease of skin sclerosis.[65] Long-wave UV radiation penetrates deep into the dermis, making it, in the opinion of the authors, the first-line therapy for the limited form of LoS. In contrast, UV radiation is not suitable for types involving deeper structures such as adipose tissue, fascia, muscles, and bones (Figure 1).

PUVA phototherapy

Due to the absence of gastrointestinal side effects associated with oral therapy using 8-methoxypsoralen, bath PUVA phototherapy has been predominantly performed in LoS. In addition to several case reports, there are currently two retrospective case series.[66,67] The larger study, published in 2013, included 28 patients (PUVA three times weekly). In 39% of cases, complete resolution was observed, clinical improvement in 50%, and no response in 10%.[67]

Similarly positive outcomes have been reported for cream PUVA phototherapy in LoS.[68] Controlled studies have not been conducted, but a recently published retrospective study showed no statistical differences in the effectiveness of PUVA and UVA1.[69] According to the authors of this guideline, bath PUVA phototherapy should be employed, particularly in the early inflammatory phase of limited LoS. A treatment cycle should consist of approximately 30 individual sessions 2–4 times weekly.

There is currently no data available for the use of balneophototherapy (sole-photo-therapy) for LoS, which is often employed in clinical practice in Germany for psoriasis.

Broadband UVA phototherapy

To date, three prospective studies on the use of broadband UVA (320–400 nm) in LoS have been published, with the largest study involving a total of 63 patients.[70] Controlled studies on broadband UVA phototherapy and comparisons with other UV modalities have not been conducted. According to the personal experience of the authors of this guideline, broadband UVA is less effective than PUVA or UVA1 and should therefore only be used if PUVA or UVA1 phototherapy is not available.

UVA1 phototherapy

The development of a lamp emitting in the range of 340–400 nm laid the foundation for modern UVA1 phototherapy in 1981.[71] Typically, lamps with an emission peak at around 370 nm are used.[72,73] Three different dosages are distinguished: low-dose UVA1 (10–20 J/cm^2), medium-dose UVA1 (>30–80 J/cm^2), and high-dose UVA1 (>80-130 J/cm^2). All three dosage regimens have been used for the treatment of LoS. In the first prospective study on UVA1 phototherapy, high-dose UVA1 was found to be highly effective, whereas low-dose UVA1 showed no substantial effects.[72] However, in several subsequent prospective studies, both low-dose and medium-dose UVA1 were effective, with medium-dose UVA1 being predominantly used in these studies.[51,69,73–85] In the only randomized controlled study on UVA1 phototherapy in LoS, medium-dose UVA1 was found to be more effective than low-dose UVA1.[86] Whether patients with darker skin types respond less favorably to UVA1 phototherapy remains unclear.[87,88] Up to 50% of patients treated with UVA1 experience a relapse within 3 years.[89] In these cases, a further UV cycle should be considered. According to the authors of the guideline, medium-dose UVA1 should be preferred, administered 3–5 times weekly for a total of 30 sessions.

Narrowband UVB Phototherapy

Narrowband UVB (peak at 311 nm) is an effective and widely available phototherapy, primarily used for the treatment of psoriasis. Data on the effectiveness of narrowband UVB in LoS include individual case reports and information from a controlled study comparing 19 patients treated with narrowband UVB (starting dose was 0.1 J/cm^2 for skin type II and 0.2 J/cm^2 for skin type III, then increased as with psoriasis) with both low-dose and medium-dose UVA1.[86] Significant improvement in the clinical score was observed in all three arms of the study; however, narrowband UVB was less effective than medium-dose UVA1. According to the authors, narrowband UVB may be considered for the treatment of LoS when UVA1 is not available. Unfortunately, UV therapy is not covered in the statutory health insurance catalog for LoS.

Laser treatment

Recommendation	Strength	Consensus strength
Pulsed dye laser (PDL) and fractional laser (CO_2 laser) *may be considered* for the treatment of LoS in types with limited skin involvement if standard UV and topical therapies are contraindicated or have not been effective.	0	100% Strong consensus

Various laser treatments have been described for the treatment of LoS. These include pulsed dye laser (PDL), excimer laser, fractional lasers such as CO_2 laser and erbium-YAG laser, Alexandrite laser, and neodymium-YAG laser.[90]

Pulsed dye laser (PDL)

The successful use of PDL in LoS was first reported more than 20 years ago. PDL (585 nm, 5 J/cm^2 twice a month) was initially employed based on experiences with hypertrophic scars, demonstrating significant clinical improvement after four sessions in a patient with morphea (plaque-type).[91] To date, a total of eight reports on PDL use are available, including individual case reports and a case series involving 26 patients and ten healthy controls.[92] In this series, 50% of patients experienced a complete resolution of skin indurations, and 27% showed mild improvement. Alongside clinical improvement, a histological reduction in collagen fiber thickness was observed, interpreted by the authors as PDL-induced shrinkage of collagen bundles. Additionally, a significant increase in CD34$^+$ dermal dendritic cells was observed after PDL. It is essential to note critically that some other case reports described facial types of LoS initially misinterpreted as vascular lesions and treated with PDL. While there was a reduction in erythema, subsequent sclerosis development could not be prevented.[90]

Fractionated lasers (CO_2 laser and Erbium-YAG laser)

Fractionated CO_2 lasers are based on the absorption of wavelengths by water, generating microscopic holes in the skin surface through laser vaporization to stimulate re-epithelialization and wound healing. In LoS, collagen neosynthesis and the induction of matrix metalloproteinases and growth factors are considered central mechanisms. Twenty-four cases of LoS treated successfully with fractionated laser therapy are reported in the literature. In addition to case reports, a study involving 17 patients compared the use of CO_2 laser with low-dose UVA1. In this study, better results were found for CO_2 in clinical, histopathological/immunohistochemical, and sonographic outcomes.[93] Moreover, CO_2 laser treatment resulted in higher patient satisfaction and a lower rate of post-inflammatory hyperpigmentation, although the pain rate within the first 24 hours was higher than with UVA1.

Regarding Erbium-YAG lasers, which act even more superficially than CO_2 lasers, there are only a few case reports describing long-lasting remissions or significant clinical improvements, involving two patients with LoS lesions on the legs and one case of Parry-Romberg syndrome.[94]

For further information, see longversion of the guideline.

Systemic treatment

Recommendation	Strength	Consensus strength
We recommend methotrexate (MTX) (off-label) as the first-line systemic therapy for LoS with severe skin and/or musculoskeletal** involvement.	↑↑	100% Strong consensus
We recommend a treatment duration of at least 12 months with methotrexate after achieving remission.	↑↑	100% Strong consensus
After achieving therapeutic success, a dose *reduction may be considered*.	0	100% Strong consensus

**Arthritis, myositis, osteitis, or depending on the severity, musculoskeletal pain symptoms attributable to LoS.

Recommendation	Strength	Consensus strength
We suggest considering systemic glucocorticosteroid therapy in addition to the systemic treatment with MTX during the active phase of LoS.	↑	100% Strong consensus

Recommendation	Strength	Consensus strength
We suggest using mycophenolate mofetil, mycophenolic acid, or abatacept as a second-line systemic therapy for LoS in cases of MTX and steroid-refractory courses, contraindication, or intolerance (off-label).	↑	100% Strong consensus

Systemic glucocorticosteroids

The effectiveness of systemic steroids in the acute phase of the disease has been described in several studies, both as monotherapy and combination therapy.[95] Their use was reserved for more severe cases, i.e., in cases of progressive generalized or linear LoS, including the subtype *en coup de sabre*. Typically, eosinophilic fasciitis responds well to steroids, and in a majority of patients with this subtype, monotherapy with systemic glucocorticoids is sufficient.[96] Additional studies on the use of systemic steroids in LoS were conducted in combination with methotrexate (see the following section). According to the authors, systemic steroids should therefore be used as monotherapy only briefly in the early acute phase of severe types of LoS due to their known side effect profile.

Methotrexate

The best available data for systemic therapy in LoS exists for methotrexate (MTX). In addition to numerous retrospective

studies[97–101] and non-controlled prospective studies[102–104] there is also a placebo-controlled multicenter study.[105] In one study, up to 28% of patients treated with MTX experienced a recurrence after the end of therapy, starting on average 1.7 years later.[106]

Dosage regimens for MTX-steroid combination therapy:
In the studies described above, different dosages for MTX and glucocorticoids were used. Within the framework of the *Childhood Arthritis and Rheumatology Research Alliance* (CARRA), three different "treatment pathways" for juvenile localized scleroderma (JLS) were first established in 2012:

1. MTX monotherapy,
2. MTX-steroid pulse therapy with intravenous methylprednisolone,
3. MTX-steroid pulse therapy with oral MTX and prednisone.[107]

These dosage regimens are integrated into the treatment recommendations of this guideline (Figure 1).

Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits lymphocyte proliferation as well as various mesenchymal cells (for example muscle cells and fibroblasts).[100] In 2009, MMF was first described as a treatment alternative for cases of LoS refractory to both MTX and steroids.[108] All patients described in the initial study experienced clinical improvement (reduction in peripheral erythema, reduction in sclerosis), and concomitant steroid dose could be significantly reduced in some cases. Since then, the effectiveness of MMF has been reported in numerous uncontrolled studies.[109–111] Based on the current data, MMF is considered a second-line therapy in the systemic treatment of LoS if MTX is ineffective or contraindicated.

Abatacept

Abatacept is a recombinant fusion protein approved for use in combination with MTX for rheumatoid arthritis, juvenile idiopathic arthritis, and psoriasis arthritis. The effectiveness of abatacept has been described in both active skin and musculoskeletal involvement in LoS.[112] A recently published multicenter study on abatacept in therapy-refractory LoS showed an overall response rate of 83%, with response lasting more than 18 months in 61% of cases.[113] Additionally, the effectiveness of abatacept has been reported in severe pansclerotic LoS as well.[114] The authors of this guideline recommend the use of abatacept as a second-line therapy, either as a monotherapy or in combination with MTX, MMF, or glucocorticoids.

Janus-kinase inhibitors

The spectrum of indications for Janus kinase (JAK) inhibitors, in addition to the many applications in rheumatology, is steadily expanding in dermatology (for example atopic dermatitis, alopecia areata). The Janus-kinase is involved in TGF-beta-mediated signaling, and activation of the JAK/STAT cascade leads to the induction of fibrosis.[115,116] Additionally, JAK induces the phosphorylation of STAT proteins, which, in turn, leads to the transcription of profibrotic and proinflammatory genes.[117] This makes JAK inhibitors an interesting approach in the management of sclerosing skin diseases. In a recently published review article, all previous case reports on JAK inhibitors in LoS were compiled.[118] It was observed that, under tofacitinib, ruxolitinib, and baricitinib, there was, in some cases, a better response compared to traditional standard therapies in all compartments (for example erythema, sclerosis, ulcerations). Although prospective and controlled studies are still lacking, the authors of this guideline think that JAK inhibitors may be considered on a case-by-case basis, weighing all known risks, in cases of refractory LoS after the use of MTX, MMF, or abatacept.

Tocilizumab

Tocilizumab is a monoclonal antibody directed against the soluble interleukin 6 (IL-6) receptor, primarily approved for chronic polyarthritis. The substance has also shown significant effects on skin involvement in systemic sclerosis.[119] Since elevated IL-6 levels were detected in the serum of patients with LoS, tocilizumab has been used for this indication as well. A case series and individual case reports described in the literature (approximately 20 cases in total) suggest the effectiveness of tocilizumab in LoS.[120–126] According to the authors opinion, tocilizumab should primarily be offered to patients with accompanying or predominant extracutaneous involvement (for example arthritis) if other standard therapies have failed or are contraindicated.

For further information, see longversion of the guideline.

Surgical therapy

Recommendation	Strength	Consensus strength
We suggest that functionally necessary surgical interventions for the linear type of LoS should be primarily performed during the inactive phase.	↑	> 75% Consensus

Recommendation	Strength	Consensus strength
Plastic surgical interventions *may be considered* during the inactive phase for linear LoS of the "en coup de sabre" type or progressive facial hemiatrophy.	0	100% Strong consensus

Orthopedic-surgical interventions, such as surgical correction for achilles tendon lengthening or correction of plastic-aesthetic deficits in the facial area, are indicated only in linear LoS.

However, it is crucial to perform these interventions only in the inactive stage of the disease, preferably several years after the end of disease activity, to minimize the risk of relapses. In cases of suspected disease activity, perioperative immunosuppressive systemic therapy should be considered.

Epiphysiodesis on the healthy leg to equalize leg length discrepancies must be performed and guided by a pediatric orthopedic specialist during the child's growth phase, for example in the pre-pubertal growth spurt.

Autologous fat transplantation, plastic surgical interventions, and the implantation of "defect-compensating" substances (for example fillers) can be used for cosmetic reasons in linear LoS of the "en coup de sabre" type or progressive facial hemiatrophy.

A particularly nuanced approach is necessary for the treatment of asymmetries in the facial area. Patients often experience significant distress due to aesthetically noticeable asymmetries and the associated stigmatization. Besides scarring changes in the skin, there are frequently deviations in skeletal symmetry in many cases. To correct these asymmetries, a combination of established procedures in oral and maxillofacial surgery has proven effective. After clinical verification of the bony asymmetry, three-dimensional imaging (computed tomography with 1 mm slices) is performed to confirm the clinical suspicion. Using the dataset, a 3D plan is created to precisely calculate the bony deficit by mirroring the healthy side onto the affected side. Subsequently, a patient-specific implant made of biocompatible materials (for example Bioverit II, Polyetheretherketon/PEEK) is manufactured.

Such implants have been used for many years in neurosurgery and oral and maxillofacial surgery to correct traumatic and congenital bone deficits in the skull and have proven highly effective in clinical practice.[127–129]

After successful integration, if needed, a further step can be taken to achieve symmetry in the soft tissue. This soft tissue augmentation is also recommended in cases where there is no primary bony deficit. Thinning atrophic skin areas can be leveled with surrounding dermal tissue through injection.

Autologous fat stem cell transplantation

Recommendation	Strength	Consensus strength
We suggest considering autologous fat stem cell transplantation for correcting soft tissue defects in the head area in cases of linear LoS.	↑	> 75% Consensus
This procedure can be performed during the inactive or active phase of LoS and under systemic therapy.	Statement	> 75% Consensus

Autologous fat stem cell transplantation (AFT) is particularly used in linear types of LoS in the head/face area. Good experiences have been reported, especially with the application of microfat.[130–132] Microfat stands out due to its low absorption rate compared to conventional fat grafts, as well as its more targeted application and a higher proportion of fat stem cells. In addition to aesthetic improvement AFT also leads to immunomodulatory and angiogenetic effects. Furthermore, anti-fibrotic effects have been demonstrated through the downregulation of extracellular matrix proteins and increased induction of collagenase activity.[130,132–134] AFT can be used in addition to ongoing systemic therapy or as a subsequent therapy for LoS.

Even though the desired result in this type of soft tissue correction for more pronounced LoS types can only be achieved through multiple sessions (usually 2–3 sessions), it offers significant advantages through the positive influence on skin quality and the long-term assurance of augmentation results compared to conventional soft tissue augmentations with hyaluronic acid injections, which are usually completely absorbed within 3–6 months.[135]

While further studies on optimal dosage and timing would be desirable, according to the guideline authors, AFT can be considered as an additional treatment option for linear LoS in the head area.

Physiotherapy

Recommendation	Strength	Consensus strength
We recommend physical therapy and manual therapy in all subtypes of LoS with restricted mobility (for example joint contracture, muscle imbalance [atrophy/hypotrophy]) and for the prevention of joint contracture in cases of skin involvement spanning the joint. This should be considered as a supplementary measure to local or systemic therapy, and therapies should be prescribed as needed.	↑↑	100% Strong consensus

Recommendation	Strength	Consensus strength
We recommend that connective tissue massage and manual lymphatic drainage be performed concurrently or following a therapy in the sclerotic stage.	↑↑	100% Strong consensus

Physical therapy is a crucial component in the multimodal treatment of the disease and is frequently employed in clinical practice. Specifically, linear, generalized, deep, and mixed types of LoS should undergo physiotherapeutic intervention, with the caveat that physiotherapy should be avoided only during the acute inflammatory phase. Connective tissue massage and manual lymphatic drainage should be administered concurrently with systemic therapy or following its completion in the sclerotic stage. The authors recommend one to two therapy cycles per week for a duration of at least 3 months. Physiotherapeutic exercises and muscle strengthening are necessary for linear types affecting the extremities, leading to contractures and restricted mobility.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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