Received: 4 December 2023 | Accepted: 22 March 2024

DOI: 10.1111/jdv.20083

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

GUIDELINES

EuroGuiderm guideline on lichen sclerosus—Treatment of lichen sclerosus

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Abstract

Introduction: Lichen sclerosus (LS) is an inflammatory skin disease affecting all ages. LS typically involves the anogenital site where it causes itching and soreness; it may lead to sexual and urinary dysfunction in females and males; however, it may be asymptomatic. First signs of LS are usually a whitening of the genital skin, sometimes preceded by redness and oedema; fissuring, scarring, shrinkage and fusion of structures may follow in its course. LS is associated with an increased risk of genital cancer. LS has a huge impact on the quality of life of affected patients, and it is important to raise more awareness of this not uncommon disease in order to diagnose and treat it early.

Objectives: The guideline intends to provide guidance on the diagnostic of LS (part 1), highlight important aspects in the care of LS patients, generate recommendations and treatment algorithms (part 2) on topical, interventional and surgical therapy, based on the latest evidence, provide guidance in the management of LS patients during pregnancy, provide guidance for the follow-up of patients with LS and inform about new developments and potential research aspects.

Materials and Methods: The guideline was developed in accordance with the EuroGuiDerm Methods Manual *v1.3* https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html. The wording of the recommendations was standardized (as suggested by the GRADE Working Group). The *guideline* development group is comprised of *34* experts from *16* countries, including *5* patient representatives.

Results: Ultrapotent or potent topical corticosteroids in females and males, adults and children remain gold standard of care for genital LS; co-treatment with emollients is recommended. If standard treatment fails in males, a surgical intervention is recommended, complete circumcision may cure LS in males. UV light treatment is recommended for extragenital LS; however, there is limited scientific evidence. Topical calcineurin inhibitors are second line treatment. Laser treatment, using various wave

For affiliations refer to page 29.

lengths, is under investigation, and it can currently not be recommended for the treatment of LS. Treatment with biologics is only reported in single cases.
Conclusions: LS has to be diagnosed and treated as early as possible in order to minimize sequelae like scarring and cancer development. Topical potent and ultrapotent corticosteroids are the gold standard of care; genital LS is often a lifelong disease and needs to be treated long-term.

The recommendations are presented throughout this guideline as displayed below: alongside the wording of the recommendations the arrow(s) and colours indicate the direction and the strength of each recommendation. The rate of agreement (consensus strength) is also displayed as the actual percentage and in form of a category-type pie-chart.

The wording of the recommendations was standardized, Table 1 (as suggested by the GRADE Working Group[1]).

INTRODUCTION INTO TREATMENT

Aims of treatment

Apart from individual treatment goals, the therapeutic approach should in general be multidimensional and aim at:

1. Rapid improvement of symptoms such as pruritus, pain or burning.
2. Maintenance or improvement of quality of life including sexual life or voiding.
3. Disease control looking at signs of disease to avoid, that is, scarring, resorption of structures, skin atrophy and malignant transformation.
4. Reduction of flare-ups.
5. Cure of LS in males.

For each patient, the aims of treatment have to be assessed individually. In the course of the disease, these aims have to be reassessed from time to time.

Assessment of the treatment success

Treatment success should be based on both patient-reported outcome measures (PROMs) to assess treatment goals (1), (2) and (4) and on clinician-related outcome measures to address treatment goal (3). To date, however, there is no consensus as to which assessment tools are to be used for this purpose.[2,3]

The Core Outcomes for Research in Lichen Sclerosus (CORALS) project is an interdisciplinary and interprofessional ongoing initiative to establish the most important outcomes to be measured in future trials of genital LS.[4] However, these outcomes 'patient-reported symptoms, clinical (visible) signs and quality of life specific to LS' may also be useful features to be evaluated at each visit in clinical practice. It will vary as to how this will be performed; an initial photograph at presentation is thought to be very helpful.

During follow-up visits, the treatment success (and potential side effects) may be assessed by longitudinal comparison of the items listed below. An initial photograph seems inevitable for comparison of the possible progression of the disease; notes regarding important aspects have to be taken on an individual base:

Assessment of treatment:

(a) Symptoms:
Intensity, 0–10 Numerical Rating Scale (NRS), and duration of itch, pain, burning, soreness and discomfort.
(b) Signs:
Erythema, oedema, hyperkeratosis, pallor/hypopigmentation, haemorrhages/ecchymoses, fissures, erosions, ulcerations, sclerosis, fusion of structures, that is, clitoral hood fusion, narrowing of the introitus, fourchette web, labial fusion in women, phimosis and sclerosis of the frenulum in men, meatal and urethral strictures, perianal involvement. Ideally using a grading scale (e.g., Meuli, 1994[5]): 1° foreskin can be retracted but shows a narrowing ring, 2° glans is partially visible, 3° meatus is visible, phimosis 4° pin hole.

TABLE 1 Wording of recommendations.

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We **recommend** . . .'	↑↑	We believe that all or almost all informed people would make that choice.
Weak recommendation **for** the use of an intervention	'We **suggest** . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not.
No recommendation with respect to an intervention	'We **cannot make a recommendation** with respect to . . .'	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting data or conflicting outcomes, etc.)
Weak recommendation against the use of an intervention	'We **suggest against** . . .'	↓	We believe that most informed people would make a choice against that 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 that intervention.

(c) Sexual aspects:
Dyspareunia, anorgasmia, erosions/fissures due to sexual intercourse, erectile dysfunction in men

(d) Urological aspects:
- Dysuria, pain of the bladder (abacterial cystitis)
- Lower Urinary Tract Symptoms (LUTS) and urethral strictures (meatus)

(e) Gynaecological aspects:
Vaginal discharge/bleeding and menstrual problems in women

(f) Other aspects:
- (In)tolerance of topicals, including emollients
- Irritant and/or allergic contact dermatitis, signs of infection
- Psychological aspects, particularly in young adolescents starting to be sexually active

Clinical severity scales to allow intra- and interindividual comparison of treatment response are still an unmet need in the context of LS.[6] For this purpose, the Clinical Lichen Sclerosus Score (CLISSCO) consisting of 3 'Symptoms', 3 'Signs' and 6 'Architectural changes' rated on a 0–4 point Likert scale was recently proposed (for vulvar LS only).[6]

After the initial treatment of usually 3 months and subsequent revision and counselling, the intervals of follow-up visits strongly depend on the activity, subjective burden and severity of LS. At each visit the type, amount and place where the creams have to be applied need to be explained:

- In more active disease, follow-up visits every 3–6 months may be indicated. In selected cases, experiencing intense symptoms visits may be scheduled more frequently.
- In long-term controlled disease, annual visits may suffice to re-adjust topical treatment and check for signs of inflammation and malignant transformation.

TREATMENT

Skin care and basic therapy

We **recommend** the use of topical ointments instead of creams or gels in lichen sclerosus patients.	↑↑	>75% agreement (11/12) Expert Consensus
We **cannot make a recommendation** in favour of wearing silk rather than cotton briefs for lichen sclerosus patients.	0	100% agreement (15/15) Expert Consensus
We **suggest** avoidance of trigger factors (mechanical factors such as trauma, unnecessary surgical interventions, piercings) and irritants (excessive water exposure or cleansing products, synthetic and tight clothing, use of wet wipes, etc.) at the affected sites in lichen sclerosus patients.	↑	100% agreement (15/15) Expert Consensus
We **suggest** regular change of incontinence pads/absorbent pads and urine-soaked undergarments to maintain dry conditions as much as possible, as well as careful management of urine incontinence in lichen sclerosus patients.	↑	100% agreement (15/15) Expert Consensus
We **cannot make a recommendation** concerning the use of oral contraceptives in females with lichen sclerosus.	0	100% agreement (14/14) Expert Consensus
We **suggest** to avoid the application of over the counter medications, lenitive herbal products, topical antihistamines and anaesthetics and perfumed products due to an increased risk of inducing contact sensitization in lichen sclerosus patients.	↑	100% agreement (23/23) Expert Consensus
We **recommend** reassuring adherence to adequate treatment and ruling out other causes such as allergies, infections and malignancy if the clinical picture worsens or symptoms like itch or pain increase.	↑↑	100% agreement (13/13) Expert Consensus

Introduction

Sites affected by anogenital LS are anatomically prone to moisture, friction and occlusion. Maceration and fissuring in LS may be worsened by contact with local irritants, for example, sweat, urine, vaginal discharge, menstrual blood, cleansing products like soap and underwear.

Contact allergy is another potential aggravating factor for itch and irritation.

Furthermore, the anogenital site is susceptible to fungal, bacterial and viral infections; these may worsen and alter symptoms and the clinical course of LS.

General advice to patients with anogenital LS

- Attention to personal hygiene is important but patients should avoid local application of irritating soaps, shampoos and bubble baths. It is strongly recommended that simple emollients are used as soap substitutes.[7]
- Application of a skin barrier ointment before swimming, bathing or voiding to protect the skin may be useful.
- Regular application of a barrier emollient to protect against local irritants is particularly important in LS patients who are incontinent of any degree, even if minor.[8]
- On anogenital skin, ointment preparations are preferred to creams because they contain less contact sensitizers, are less irritant, allow better skin penetration and provide a better barrier effect.[9]
- Tight-fitting garments should be avoided. One controlled randomized double-blind study reported that patients undergoing treatment for LS had fewer symptoms when wearing silk rather than cotton underwear.[10]

Silk underwear

A controlled randomized study showed that women undergoing treatment for LS have fewer symptoms when wearing silk rather than cotton briefs.[10] However, results may be biased because the study was financially supported by the manufacturer; furthermore, it is difficult to perform a masked controlled trial, because the difference between silk fabrics and cotton cannot be hidden. Further studies are needed to verify the effect of silk underwear in genital LS.

Avoidance of triggering factors (see chapter trigger factors in part 1 of the guideline or in the long version)

Mechanical factors, including friction due to tight clothing, sexual abuse, surgery, radiotherapy or trauma, are known to be implicated in both development and maintenance of LS lesions, due to the Koebner phenomenon.[11–14]

A moist environment and chronic irritation from urine exposure due to occlusion and/or urinary incontinence have been increasingly recognized as trigger factors for LS development and/or LS maintenance. The role of occlusion has been supported by Gupta et al., based on the observation that only the opposing surfaces of glans in men and vulva in women were affected in early stages of the disease, while non-occluded sites were spared.[15] An association between urinary incontinence and LS was initially described by Owen and Yell in a study of seven women, four of whom experienced clearance of LS following control of the incontinence.[16] In addition, a retrospective study suggested that urinary incontinence may be implicated also in the development of paediatric vulval LS.[17] The role of urine and occlusion has been further supported by studies on LS affecting perineal urethrostomies, urostomies and peristomal LS, as well as on males with a history of urological interventions and microincontinence.[18–20]

Obesity, arterial hypertension, coronary artery disease, diabetes mellitus and smoking have also been associated with the development and chronicity of LS.[21,22]

The role of infectious agents, particularly Borrelia burgdorferi, human papilloma virus, hepatitis C and Epstein–Barr virus, has yet to be elucidated.[23–25]

Finally, disturbance of the androgen-dependent growth of the vulval skin by oral contraceptives, especially those with anti-androgenic properties, has been suggested to trigger early onset LS in young women.[26]

Risk of contact allergy

Studies looking at the prevalence and risk of complicating contact allergy in patients with LS are sparse and characterized by low numbers of included LS patients. Two early studies found relevant reactions when patch testing in 9/19 (47%) and 7/16 (44%) LS patients, respectively.[27,28] The allergens involved included neomycin, clioquinol and cinchocaine. In a recent study, the most common allergens were fragrances, patients' own products and local anaesthetics.[29] There were no positive patch tests to corticosteroids among these LS patients.[27,29] However, in a study including 42 LS patients of 66 participants, 4.5% were found to have a positive patch test to topical corticosteroids including two LS patients.[30]

The study by Corazza et al. highlighted the frequent use of products based on botanical ingredients among women with itchy vulval diseases and pointed out that contact dermatitis is a potential adverse effect of those products.[30]

The relevance of patch test results should be carefully evaluated as a positive patch test result does not always implicate a role in aetiology of a vulval dermatitis. A few previous studies have discussed whether the finding of eosinophils or eosinophilic spongiosis in LS, when present, could be a marker for the coexistence of autoimmune bullous disease or allergic contact dermatitis. One study of 121 patients with vulval LS found that the presence of eosinophilic spongiosis, marked lymphocyte exocytosis, dermal eosinophils and excoriations predicted poor symptomatic response to treatment, and the authors recommended patch testing to rule out an additional allergic contact dermatitis in the case of such histological findings.[31] Keith et al. investigated 235 LS patients, 14% were males and 22% had extragenital, suggested an association between tissue eosinophils in LS and an associated disease, but the finding was not statistically significant. The authors concluded that the finding of tissue eosinophils alone should not lead to examination for an underlying associated disease, for example, contact dermatitis or autoimmune bullous disease, unless clinical signs of such a condition are present.[32]

Treatment of itch

In addition to pain, itch is a key symptom in genital LS; in fact, 62.3% of patients complain of itch.[33]

The pathophysiology of itch in LS is thought to be complex and multifactorial.[34] It mainly depends on inflammation and immune dysregulation; therefore, only an appropriate therapy of the underlying disease may treat this disturbing symptom which may be controlled in 80%–90% of female LS patients who correctly follow advised standard treatment (e.g., with potent topical steroids).[35]

Daily applications of emollients may positively affect itch, preserving the skin barrier integrity and making the skin softer. An open-label non-comparative study, performed in women affected by mild-to-moderate vulval LS, evaluated the efficacy of a topical product containing avocado and soybean extracts and other lenitive and anti-oxidant principles administered for 24 weeks, in association with a dietary supplement containing avocado and soybean extracts, vitamin E and para-aminobenzoic acid. Among 23 included women, the mean itch value decreased significantly at Weeks 12 and 24 compared to baseline.[36]

Based on our experience, many patients may benefit from adding itch-relieving compounds such as polidocanol 3% to emollients, but controlled studies to support this observation are

still lacking. Particular attention should be paid to sensitizers such as local anaesthetics, for example, lidocaine, and herbal products, for example, calendula and menthol which should be avoided.

Topical treatment

Emollients

We **recommend** co-treatment with topical emollients during standard therapy in women with genital lichen sclerosus.	↑↑	100% agreement (17/17) Expert Consensus
We **recommend** co-treatment with topical emollients in girls with genital lichen sclerosus.	↑↑	
We **suggest** co-treatment with topical emollients in men with genital lichen sclerosus.	↑	
We **suggest** co-treatment with topical emollients in boys with genital lichen sclerosus.	↑	
We **suggest** co-treatment with topical emollients in patients with extragenital lichen sclerosus.	↑↑	

Mechanisms of action and efficacy

Emollients may give additional symptom relief after an initial treatment with topical steroids.

An open trial of topical steroid followed by maintenance daily treatment (cold cream) in women showed that symptom relief was maintained; however, one cannot extrapolate from this that this was the effect of the emollient or a long-term effect of steroid.[37] A randomized trial of topical vitamin E cream compared to emollient following an initial treatment with topical corticosteroid showed similar relapse rates over a 1-year period; thus, vitamin E does not appear to have any advantage over an emollient.[38]

Dosage: acute and maintenance

As for the dosage, there are currently no publications available. Based on our experience, we recommend applying emollients during the acute phase at least two times a day to moisturize the skin, improve the skin barrier and make it more resistant to irritating external factors such as clothing, toilet paper, sanitary pads, urine, soaps, vaginal discharge, sweat, lubricants, semen and friction during sexual intercourse or sports. In case of vulval burning during urination, application of emollients prior to urination might help to reduce skin contact with urine. However, to avoid a diluting effect of topical steroids, emollients should better not be applied simultaneously.

Following the acute phase, the use of emollients may also be helpful to maintain the improved skin condition. Ideally, they should be applied on a daily basis or at least following the use of soaps in the genital area.

Safety and special considerations

Generally, emollients are very well tolerated and no safety concerns have been raised. However, in rare cases they may lead to irritant or allergic contact dermatitis. For example, additives such as benzoic acid, benzalkonium chloride, polyethylene glycol or sodium lauryl sulphate (SLS) are known irritants[39,40] that may be components of emollients. Likewise, benzoic acid may act as an allergen in emollients as others can such as lanolin, jojoba oil, propylene glycol fragrances and balsam of Peru belonging to the most frequent ones.[39,41] Therefore, only fragrance-free emollients should be used. In case of suspicion of an allergic contact dermatitis either standard patch testing or a repeated open application test (cubital application of the suspected topical with reading after 24 h and, if no reaction is visible, repeated daily for 7–10 days) might be a simple and helpful test for a delayed type hypersensitivity.

Topical and intralesional corticosteroids

We **recommend** ultrapotent or potent topical corticosteroids in women with genital lichen sclerosus.	↑↑	>75% agreement (16/17)[1] Evidence- and consensus-based
We **recommend** ultrapotent or potent topical corticosteroids in girls with genital lichen sclerosus.	↑↑	
We **recommend** ultrapotent or potent topical corticosteroids in men with genital lichen sclerosus.	↑↑	
We **recommend** ultrapotent or potent topical corticosteroids in boys with genital lichen sclerosus.	↑↑	
We **suggest** ultrapotent or potent topical corticosteroids in patients with extragenital lichen sclerosus.	↑	

[1]1 Abstention

Ultrapotent topical corticosteroids:
Direct evidence available for:
- Women:
  - Cochrane review (2 RCTs)
  - 5 further RCTs
    - Improvement of symptoms: GRADE ⊗⊗⊗⊗ high - ⊗○○○ very low
    - QoL: GRADE ⊗⊗⊗○ moderate - ⊗⊗○○ low
    - Sexual function: GRADE ⊗○○○ very low
    - Urinary function: GRADE ⊗⊗○○ low
    - Patient global assessment: GRADE ⊗⊗○○ low
    - Physician global assessment: GRADE ⊗○○○ very low
    - Minor adverse events: GRADE ⊗○○○ very low
  - 9 non-comparative/non-prospective studies (n = 513)
- Girls
  - 7 non-comparative/non-prospective studies (n = 155)
- Women and girls:
  - 1 RCT
    - Improvement of symptoms: GRADE ⊗⊗⊗○ moderate
- Females age unknown:
  - 1 non-comparative/non-prospective study (n = 59)
- Men:
  - 4 non-comparative/non-prospective studies (n = 104)
- Men and boys:
  - 1 non-comparative/non-prospective study (n = 185)

Potent topical corticosteroids:
Direct evidence available for:
- Women:
  - 3 RCTs
    - Improvement of symptoms: GRADE ⊗⊗⊗⊗ high - ⊗○○○ very low
    - Patient global assessment: GRADE ⊗⊗○○ low
    - Physician global assessment: GRADE ⊗○○○ very low
  - 14 non-comparative/non-prospective studies (n = 988)
- Girls
  - 1 non-comparative/non-prospective study (n = 11)
- Boys
  - Cochrane review (1 RCT)
  - 2 non-comparative/non-prospective studies (n = 83)

For specific results, see Evidence report

We recommend the use of topical steroid ointments instead of creams or lotions in lichen sclerosus.	↑↑	>75% agreement  (12/13)[1] Expert Consensus

[1]1 Abstention

We **suggest** intralesional corticosteroids to hyperkeratotic lesions in women with topical steroid-resistant genital lichen sclerosus (provided malignancy has been excluded).	↑	>75% agreement  (15/16)[1] Evidence- and consensus-based
We **cannot make a recommendation** with respect to intralesional corticosteroids in girls with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to intralesional corticosteroids in men with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to intralesional corticosteroids in boys with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to intralesional corticosteroids in patients with extragenital lichen sclerosus.	0	

[1]1 Abstention

Direct evidence available for:
- Women:
  - 1 non-comparative/non-prospective study (n = 88)

For specific results, see Evidence report

Summary: no uniform recommendation possible

- Initial treatment:
  - Clobetasol propionate 0.05% (ointment) or mometasone furoate seem similarly effective.[42] Usually a fingertip unit is used.
  - Some recommend steroid ointments once daily for 3 months; others recommend 1 month daily, then slow reduction to, for example, alternate days application after daily Rx for another 2 months.

  Aim:
  - Healing of fissures and erosions
  - Hyperkeratosis should remit almost completely
  - Sclerosis should soften: improvement of phimosis
  - Pallor and architectural changes will usually not improve
- Long-term treatment

  Aim: It is thought to prevent architectural changes and carcinoma development.[43]
  - Some recommend continuous Rx, for example, once or twice per week others treat only active disease (a RCT to investigate this is planned, 'PEARLS': https://www.fundingawards.nihr.ac.uk/award/NIHR135121).
  - Various potencies of steroids are used; there is most experience with potent or ultrapotent topical steroids.
  - There are hardly any steroid-associated adverse effects, like skin atrophy, in continuous long-term treatment observed. Usually a 30 g tube of ointment is sufficient for 1-year treatment, the steroid ointment has to be applied to the site that initially showed signs of LS.
  - Emollients should be used liberally

General introduction to the topic

This chapter deals with corticosteroids delivered by topical application and intralesional injection. Corticosteroids possess anti-inflammatory action that can reduce the inflammation of LS.[44]

Ultrapotent and potent topical corticosteroids

Mechanisms of action and efficacy. With well-established efficacy and safety, potent or very potent topical steroids like clobetasol propionate 0.05% cream or ointment are recommended as first-line treatment, both in the acute episodes and the maintenance phases.[45–47]

Potent topical corticosteroids function as an anti-inflammatory and anti-fibrotic agent. They influence multiple different signalling pathways by switching off activated (pro)-inflammatory genes.[43,44,48] They also have a rapid anti-pruritic effect.

In clinical practice, potent topical steroids rapidly improve local signs and symptoms, usually in less than 10 days.

Creams and ointments are the most frequently used vehicles as they spread easily and adhere adequately to mucosal surfaces. However, as per our experience, several different types of vehicles should be tested by the patient to find the most efficacious and comfortable treatment formulation that helps to maintain adherence. However, ointments are usually less stinging, contain less contact allergens, provide a better barrier function and usually deliver the active ingredient better to the skin than creams or lotions.

The effectiveness of ultrapotent and potent topical steroids appear comparable in the treatment of genital LS. Most studies are performed with ultrapotent steroids (clobetasol propionate); however, in certain situations modern potent steroids like mometasone furoate may be preferred, namely in children because the skin is thinner and steroid related side effects may occur more frequently with ultrapotent steroids and in pregnancy where resorption of the steroid should be avoided because of safety aspects.

Females with genital LS. About 60%–70% of LS patients achieve complete remission of their symptoms after a 3-month course of clobetasol propionate 0.05%, usually once daily application.[35,42,49] Similarly effective was mometasone furoate (MMF) 0.1% once daily after 12 weeks in a head-to-head trial, 59% and 37% of patients in the clobetasol propionate group and 67% and 48% in the MMF group achieved an improvement of at least 75% in subjective and objective scores, respectively.[42,49]

There is evidence that less potent steroids (e.g., triamcinolone and prednicarbate) are also effective as maintenance therapy and for the treatment of moderate episodes or recurrences.[43,50,51]

There are no comparative randomized trials in girls with LS; however, non-comparative studies show that

treatment with potent to very potent topical steroids is effective in suppressing signs and symptoms of LS.[52,53] In some patients, LS will go into remission after childhood; however, the course is variable and close follow-up during and after puberty needs to be assured in order to detect recurrences of LS early.[54]

Males with genital LS. Both MMF and clobetasol dipropionate are effective in treating early and intermediate penile LS, but the rate of cure is unknown. A placebo-controlled RCT assessed the efficacy of topical MMF 0.05 ointment in treating penile LS in 40 boys after 5 weeks' application.[55] MMF was found to improve the clinical grade of phimosis in 7/17 boys (41%) after 5-week treatment; no improvement was seen in late disease (the treatment was not curative, and all were circumcised after topical treatment). No local or systemic adverse events occurred in either group. A study in 56 boys found topical corticosteroids effective in mild LS limited to the prepuce only, but ineffective in those with established scar formation; LS was not proven histologically.[56]

A retrospective study in 21 men with penile LS found clobetasol dipropionate 0.05% cream effective in 16/21 (76%) (6 required circumcision) and safe with no risk of epidermal atrophy after 7-week treatment in average.[57] In total, 185 males treated with clobetasol propionate 0.05% (for about 12 weeks with decreasing frequency) were analysed retrospectively, 60% were successfully treated, with a relapse in some reducing it to 50% success rate, and the mean follow-up was 15 months.[58]

The risk of development of penile cancer in men with LS is not known.

Dosage: acute and maintenance. In clinical trials, clobetasol propionate 0.05% cream or ointment was applied once or twice daily for 3 months, or in a stepwise approach, that is, applied once or twice daily for 1 month then once daily or alternate-day treatment for 2 months; possibly depending on the severity of signs and symptoms and the age of the patient (women vs. girls).[45,49,59]

There is no consensus on the standard dosage regimen for the treatment of LS. The usual recommendation is to apply strong to very strong topical steroids for 3 months without interruption, until complete or nearly complete clinical remission is achieved, followed by either continuous treatment once or twice weekly or ad hoc treatment in case of signs of recurrence (hyperkeratosis, erythema, pruritus).[43,46] In general, ultrapotent to potent agents are used in the acute phase and initial treatment periods (1–3 months). Subsequently, the topical steroids are tapered.

Only in rare instances, there is a complete remission without recurrence. There is evidence that also less potent steroids (e.g., triamcinolone and prednicarbate) are effective as maintenance therapy and for the treatment of moderate episodes or recurrences.[43,50,51] In active disease, the dose may be increased to daily applications for 1 or 2 weeks.

Safety. Adverse effects of topical steroids are rarely seen. Rarely local irritation and burning, especially during the first treatment applications and if the skin is particularly inflamed, are experienced, this is more often observed when creams instead of ointments are used. In the long term, dryness, hypopigmentation and dermal atrophy may be observed, particularly to keratinized skin. However, topical steroids can be applied in LS over years without significant clinically relevant adverse effects. The undesirable effects of stinging, burning and xerosis are most commonly linked to the vehicle of the topical steroid rather than to the corticosteroid itself.[60]

However, it is important to point out where the topicals have to be applied and how much has to be used; for example, one fingertip unit is sufficient to treat the whole vulva. It should be pointed out that the topical steroid has to be applied to areas that are affected by LS, for example, the clitoris, the labia minora, the interlabial sulci and perineum. Topical steroids must not be applied to unaffected skin where they will cause adverse effects like erythema, irritation and dermal atrophy if continuously used.

Monitoring. There is no specific local or biological monitoring to be considered.

As there is an estimated risk for vulval intra-epithelial neoplasia (VIN) or invasive squamous cell carcinoma (SCC) of approximately 5% in affected women, lifelong follow-up annually is recommended.

Any suspicious area, such as new papules/nodules, atypical lesions or non-healing ulcers of areas involved with LS should be biopsied for histological assessment.

Intralesional corticosteroids

Intralesional injection of triamcinolone acetonide or dexamethasone may be an alternative treatment to potent topical steroids in LS for some patients.[61–63] In a 5-year study, Ventolini et al. used 5 mL per vulval site in pruritic vulval LS of a solution containing 10 mL triamcinolone 2 mg and 0.25% bupivacaine. Ultrapotent topical corticosteroids applied weekly were compared to monthly anaesthetic/corticosteroid subdermal injections combined with topical steroids.[63] The response to injections was more rapid and prolonged; however, patients were less satisfied with the injections; potent topical corticosteroids remain first line.[63] Intralesional steroid injections may be tried if there is a lack of response to potent/ultrapotent topical steroids if, for example, poor penetration (e.g., in very hyperkeratotic lesions) or a lack of compliance is considered.[62] Intralesional corticosteroid injections should be avoided in atrophic skin or in small areas as the tissue may become damaged and ulcerate.

Topical calcineurin inhibitors

We **suggest** topical calcineurin inhibitors in women with genital lichen sclerosus as second choice or as an additional treatment if topical corticosteroids are contraindicated or insufficient. (off label)	↑	>75% agreement  (15/16) Evidence- and consensus- based
We **suggest** topical calcineurin inhibitors in girls with genital lichen sclerosus as second choice or as an additional treatment if topical corticosteroids are contraindicated or insufficient. (off label)	↑	
We **suggest** topical calcineurin inhibitors in men with genital lichen sclerosus as second choice or as an additional treatment if topical corticosteroids are contraindicated or insufficient. (off label)	↑	
We **suggest** topical calcineurin inhibitors in boys with genital lichen sclerosus as second choice or as an additional treatment if topical corticosteroids are contraindicated or insufficient. (off label)	↑	
We **cannot make a recommendation** with respect to topical calcineurin inhibitors in patients with extragenital lichen sclerosus. (off label)	0	

Direct evidence available for:
- Women:
  - Cochrane review (1 RCT)
  - 6 non-comparative/non-prospective studies (n = 107)
- Girls
  - 2 non-comparative/non-prospective studies (n = 24)
- Women and girls
  - 1 RCT
    - Improvement of symptoms: GRADE ⊗⊗⊗○ moderate
- Boys
  - 1 non-comparative/non-prospective study (n = 20)

For specific results, see Evidence report

General introduction to the topic

Two topical calcineurin inhibitors (TCIs), pimecrolimus 1% cream and tacrolimus 0.1% and 0.03% ointment, licensed for the treatment of atopic eczema, are used off label to treat LS.[64–78] There are few randomized studies comparing TCIs versus clobetasol propionate in vulval LS.[70,79,80]

Mechanisms of action and efficacy

Tacrolimus is a lipophilic compound that inhibits the second messenger calcineurin and blocks the transcription of pro-inflammatory cytokines such as interleukin (IL)-2 and interferon gamma. By inhibiting calcineurin, tacrolimus also reduces antigen presentation and T-cell activation. Moreover, it affects other cell types involved in pruritus and inflammation such as mast cells, eosinophils and basophils by inhibition of IL-3, IL-8, IL-13 and granulocyte/macrophage colony-stimulating factor. On epidermal antigen-presenting cells, the FcεR1 receptor expression is reduced. While many of the pharmacological effects of topical tacrolimus parallel those of corticosteroids, side effects such as skin atrophy and telangiectasia are not observed with topical tacrolimus and pimecrolimus.[68,69]

Women with genital LS. Both groups of a double-blind, randomized trial of 38 women with biopsy-proven vulval LS showed similar improvement in pruritus and burning/pain after a 12-week treatment period with either topical pimecrolimus or clobetasol propionate.[79] Clobetasol was found to be superior in improving inflammation when compared with pimecrolimus (p = 0.015).

The relief of symptoms in LS by pimecrolimus is also supported by several case series.[65,81,82] Complete remission with relief from itch, pain and inflammation was achieved in 35% (9/26) after 2 months and in 42% (11/26) after 6 months. After 2 months twice daily application of pimecrolimus cream 1%, complete (19 of 20) or partial (1 of 20) clinical remission was obtained in 20 patients (80%). Five patients (20%) showed no clinical response. Post-treatment biopsies from 23 women showed decreased p53 staining, the number and staining intensity of Bcl-2-positive basal keratinocytes was increased. Whether the observed decrease in p53 and increase in Bcl-2 expression will provide protection from malignant progression warrants long-term follow-up.[81,83]

The Female Sexual Distress Scale (FSDS) was administered upon enrolment and at the end of the trial in women enrolled in a double-blind 12-week trial comparing clobetasol versus pimecrolimus for the treatment of LS. Thirty-one of 36 women had adequate treatment of LS as determined by a dermatopathologist's evaluation of pre- and post-treatment biopsy specimens. The mean baseline FSDS score for the clobetasol group was 29 and post-treatment it was 15 (p = 0.001). In the pimecrolimus group, the mean baseline FSDS score was 27 and post-treatment 21 (p = 0.001).[80]

A multicentre, phase II trial assessed the safety and efficacy of tacrolimus ointment 0.1% for the treatment of LS.[69] Eighty-four patients (49 women, 32 men and 3 girls) between 5 and 85 years with longstanding, active LS (79 with anogenital and 5 with extragenital LS) were treated twice daily for 16 weeks. Fourteen dropped out early. Clearance of active LS was reached by 43% (ITT 36%) of patients after 24 weeks of treatment and partial resolution by 34% (ITT 29%) of patients. Maximal effects occurred between Weeks 10 and 24 of therapy.

Virgili et al. reported 11 women with vulval LS achieving complete remission in 36% and partial remission in a further 55% after 3 months of treatment with tacrolimus ointment 0.1%.[72]

Sotiriou et al. treated 10 postmenopausal women with biopsy-proven recalcitrant vulval LS with tacrolimus ointment 0.1% twice daily for 8 weeks. Analysis of subjective scores showed a positive result of the drug on pruritus, burning and pain. Reduction of symptoms occurred within the first 2 weeks of treatment in all patients. The visual analogue scale decreased from 2.55 at baseline to 0.95 at week 8, but

only a minor influence on the hyperkeratosis, atrophy, sclerosis and depigmentation was shown. Nine out of 10 patients achieved a minor improvement in clinical signs. The treatment duration in this study was only 8 weeks, which could explain the poor clinical response.[73]

Men with genital LS. Kyriakou et al. assessed retrospectively that clobetasol propionate 0.05% cream is effective in the treatment of genital LS in males. Maintenance therapy with methylprednisolone aceponate 0.1% cream or tacrolimus 0.1% ointment suggests that there is no difference between the two in preventing relapses.[84]

TCIs in children with genital LS. There are few case series reporting treatment of LS with topical tacrolimus in children.

Three prepubertal girls and three adults were treated with 0.1% tacrolimus ointment once daily. All patients experienced complete resolution with long-lasting remission for up to 1 year.[85] Matsumoto et al. reported a 5-year-old girl with vulval LS unresponsive to mild topical corticosteroids, who was treated successfully with tacrolimus ointment 0.03% once daily with complete remission after 14 weeks.[86]

Fourteen prepubertal girls (4–11 years) with anogenital LS were treated with 0.03% tacrolimus ointment twice daily for 16 weeks; then, 9 of the 14 patients adhered to 2 times weekly for further 6 months (a total of 10 months). Clinical improvement occurred in all patients (100%). Complete response of symptoms and signs was achieved in 5 (36%), 9 (64%) and 11 (79%) patients at 8 weeks, 16 weeks and 10 months, respectively. During the follow-up period of 1 year, 4 of 5 (80%) had a recurrence of symptoms, while only 2 of 9 (22%) patients who were on maintenance therapy developed recurrence of disease.[87]

Twenty patients after penile surgery with histological confirmation of LS participated in an adjuvant treatment study. Subsequent to surgery, parents applied tacrolimus 0.1% ointment twice daily to the glans and the meatus for 3 weeks. Further, 18 patients with possible early LS were clinically followed up without any treatment. Clinical follow-up was performed up to 13 months. All 20 LS patients completed the study without any relevant side effects. Two relapses occurred and were treated with an additional 3-week cycle of topical tacrolimus 0.1% ointment. None of the 18 early LS cases progressed to full-scale LS. This study shows that tacrolimus 0.1% ointment applied immediately after surgery in fully established LS is a tolerable and most probably safe adjuvant treatment option. Median disease control in all treated individuals was >1 year.[88]

Extragenital LS. Use of topical tacrolimus on its own for extragenital LS proved to be unsuccessful[74,75] or inferior to topical corticosteroids.[70] However, treatment of extragenital LS with tacrolimus combined with UV light was successfully used in few patients.[75,84,89]

Dosage: acute and maintenance

There is no consensus on the treatment of TCIs for genital LS. The usual approach is to apply TCIs initially twice daily possibly followed by once daily, as soon as the lesions regress, for 3–6 months continously.[64,66]

TCIs may be used for maintenance therapy in girls after initial treatment with topical clobetasol 0.05% once or twice daily for several weeks. Steroids may be tapered to once daily applications on weekends and topical tacrolimus 0.1% introduced once daily during the week. With maintained clearance of lesions, clobetasol application may be discontinued and tacrolimus tapered to once daily on weekends only; this may avoid steroid induced adverse effects.[90]

Safety

There are no significant differences in reported adverse drug reactions between clobetasol and pimecrolimus, both appear well tolerated, although mild local skin reactions like burning and itching lasting for 3–14 days are reported, in particular with tacrolimus.

TCIs do not seem to induce skin atrophy, hypopigmentation, striae, telangiestasias, rebound flares or hypothalamo-pituitary adrenal axis suppression. The large molecular size of TCIs minimizes their absorption through the skin into the circulation, and therefore, their long-term use is associated with minimal systemic absorption with no evidence of systemic accumulation in adult and paediatric pharmacokinetic studies.[76] The blood concentrations of pimecrolimus were checked in 10/26 patients (39%) and were undetectable in all cases, and there were no systemic adverse reactions.[65]

Infections such as genital herpes and vulvovaginal candidiasis both occurred in 2% of patients treated with tacrolimus. No malignancy was observed during an 18-month follow-up period.[69] The immunosuppressive effect of topical tacrolimus may have triggered bacterial vaginosis in the context of LS in a 10-year-old girl.[91]

The theoretical safety concern (observed in an animal study) that TCIs may increase the risk of lymphoma and other cutaneous malignancies is not supported by multiple case–control, meta-analysis studies and post marketing registries.[77,78]

In conclusion, TCIs twice daily for at least 12 weeks have some effect in suppressing symptoms (pruritus, burning, dyspareunia) in LS; however, clinical signs are usually better treated by potent topical steroids.[11,70] Both topical tacrolimus[64,69,71–74] and pimecrolimus[65,71,72,74] are reported to control vulval LS; they are suggested in females with corticosteroid-resistant disease or intolerance to steroids.[47]

However, in boys and men, surgical therapy may be more appropriate as a second choice.

The long-term use and effect of TCIs in LS is not well investigated.

Topical retinoids

We **cannot make a recommendation** with respect to topical retinoids in women with genital lichen sclerosus. (off label)	0	100% agreement  (21/21) Evidence- and consensus- based
We **cannot make a recommendation** with respect to topical retinoids in girls with genital lichen sclerosus. (off label)	0	
We **cannot make a recommendation** with respect to topical retinoids in men with genital lichen sclerosus. (off label)	0	
We **cannot make a recommendation** with respect to topical retinoids in boys with genital lichen sclerosus. (off label)	0	
We **cannot make a recommendation** with respect to topical retinoids in patient with extragenital lichen sclerosus. (off label)	0	
Direct evidence available for: • Women: ○ 3 non-comparative/non-prospective studies (n = 50) For specific results, see Evidence report		

Introduction

Retinoids induce changes in both the dermis and epidermis. Many of their tissue effects are mediated by their interaction with two families of nuclear receptors, the retinoid acid receptors (RARs) and retinoid X receptors (RXRs).[92] An imbalance in the expression of nuclear RARs, namely of RAR-α and RAR-γ, has been postulated to be involved in the pathogenesis of vulval LS.[93]

Mechanisms of action and efficacy

There are few case series reporting topical retinoids in the treatment of LS.

In an open, uncontrolled clinical study Virgili et al. treated 22 patients with vulval LS with topical 0.025% tretinoin once a day 5 days per week for 1 year. Cessation of itch was observed in 76%, 19% improved. In total, 75% had no more burning sensations, and 78% had no more pain with sexual intercourse (11% had less pain). Clinical scores improved in 58% showing complete remission of hyperkeratosis, and 21% had partial remission. Sclerosis went into complete remission in 5% and partially in 35%; erosions heeled completely in 50% and partly in 25%. Remission was obtained up to 12 months post-therapy in 13 patients (4–13; average 7 months); one patient reported a recurrence in month 13.[94]

An 84-year-old women was treated with topical 0.01% tretinoin twice daily for the first month followed by 0.025% topical tretinoin. Two months later, the pruritus and clinical appearance had improved.[95]

Topical application of 13-cis-retinoic acid (0.5% cis-retinoic acid in ointment) resulted in complete disappearance of LS signs in 11 of 20 patients with LS (6 partial, 3 no response) usually after 1–2 months of daily retinoid application. Maintenance treatment followed for 2–4 months once or twice weekly. Follow-up off treatment 4–9 months later showed no recurrence.[96]

0.025% topical tretinoin applied with an alternate-day regimen for a period of 24 weeks induced an improvement of at least 75% in subjective and objective scores, respectively, in 35.3% and 17.6% of vulval LS patients (n = 17).[97] Moreover, 35.3% and 58.8% of patients achieved an improvement in Global Subjective Score (GSS) of at least 75% and 50% compared with baseline, respectively. Mean scores of itching, leukoderma (pallor) and hyperkeratosis decreased significantly in the study patients.

A retrospective, open-label, nonrandomized, comparative cohort study compared the efficacy and tolerability of 12-week MMF 0.1% ointment plus tretinoin 0.05% cream short contact therapy versus MMF 0.1% ointment plus a cold cream in active vulval LS. An improvement of at least 75% in subjective and objective scores was achieved in 50% and 61.1% of patients in the former group, respectively, compared with 100% and 63.1% in the second group. The combination of MMF with a topical retinoid did not enhance the effectiveness of MMF.[98]

An interesting observation is described by Kaya et al. CD44-targeted deficiency in mouse epidermis results in LS-like histological picture.[99] In human genital and extragenital LS lesions, the epidermal expression of CD44 is decreased or absent, both at the protein and mRNA levels, which is correlated with an accumulation of hyaluronate in the superficial dermis. This suggests that LS might result from an epidermal damage of unknown origin, responsible for a progressive decrease in keratinocyte CD44, subsequently leading to dermal changes in which hyaluronate accumulation is a conspicuous feature.[100] It was hypothesized that restoring epidermal CD44 expression might be a therapeutic target in LS. The topical application of retinoids dramatically increases epidermal CD44 expression at both the protein and mRNA levels in murine and human skin.[101] Retinaldehyde 0.05%, a precursor of precursor of retinoids, strongly inducing CD44 when applied on murine and human skin, was applied twice daily to histologically proven LS of the vulva in one patient. After 1-month application, significant clinical improvement was observed with the disappearance of the histological characteristics of the disease and the presence of an epidermal hyperplasia; CD44 expression in the epidermis was completely restored and dermal hyaluronate disappeared.[101] A double-blind parallel trial in 20 adult patients with biopsy-proven vulval LS comparing MMF plus retinaldehyde with MMF plus placebo for 6 months did not allow exploration of the effect of retinaldehyde monotherapy and lacked potency to demonstrate strong synergy with MMF.[102] It is suggested that agents with the potential of increasing epidermal CD44 should be tried in LS.

Safety

Side effects, mainly mild erythema and burning, are reported in about 35% of patients.[97] Seldom patients discontinue treatment due to adverse effects.

Special considerations

Premenopausal women should use contraception when treated with topical retinoids.

Treatment of vulval LS with topical retinoids is thought to have a beneficial effect, and retinoids may be tried if topical steroids fail to reduce hyperkeratosis and may be considered as additional treatment. However, retinoids should not be regarded as alternative to topical steroids and calcineurin inhibitors.

Topical hormone preparations

We **recommend against** topical testosterone and topical dihydrotestosterone in women as a treatment for genital lichen sclerosus.	↓↓	100% agreement (16/16) Evidence- and consensus- based
We **recommend against** topical progesterone in women as a treatment for genital lichen sclerosus.	↓↓	
We **recommend against** topical oestrogen on the vulva in women as a treatment for genital lichen sclerosus. However, women may have additional genitourinary syndrome in which topical vaginal oestrogens may be helpful.	↓↓	
We **recommend against** topical hormone preparations in girls as a treatment for genital lichen sclerosus.	↓↓	
We **recommend against** topical hormone preparations in men as a treatment for genital lichen sclerosus.	↓↓	
We **recommend against** topical hormone preparations in boys as a treatment for genital lichen sclerosus.	↓↓	
We **recommend against** topical hormone preparations in in patients as a treatment for extra-genital lichen sclerosus.	↓↓	

Direct evidence available for:
- Women:
  - Cochrane review (5 RCTs with testosterone, dihydrotestosterone, progesterone)
  - 1 RCT (testosterone)
    - Improvement of symptoms: GRADE ⊗○○○ very low
  - 4 non-comparative/non-prospective (testosterone *n* = 80); progesterone (*n* = 60); clobetasol propionate + estradiol (*n* = 17)

For specific results, see Evidence report

Hormonal receptors of the vulva

The assumed higher incidence of LS in peri- and postmenopausal women suggests a pathogenic role of sex hormones in LS. In an early study by Friedrich in 1984, free serum testosterone and androstenedione were significantly decreased in patients with untreated vulval LS; an abnormal 5 alpha-reductase activity in these patients was suggested.[103] Consequently, topical testosterone 2% was used in female LS patients and showed remission of LS in a subgroup of patients, but androgenic side effects like clitoral enlargement, hirsutism, acne vulgaris and amenorrhoea were common and unacceptable.[103–105] In normal female genitals, the transition from vagina to vulva is marked by an increase in androgen receptors and a decrease in oestrogen and progesterone receptors.[106] Whether there is a pattern of altered hormone receptor expression or even loss or increase in LS tissue is not clear, but androgen receptors expression seems to be decreased.[107,108] It has been suggested that disturbance of the androgen-dependent growth of the vulval skin by oral contraceptives (OCP) and especially by OCPs with anti-androgenic properties might trigger the early onset of LS in a subgroup of susceptible young women.[26] In contrast, progesterone-only methods for contraception were also negatively associated with vulval LS.[109]

Several findings support the influence of a hormonal pathogenesis in LS, which might be important for the treatment of the disease. A regulatory role of sex hormones regarding immunology and repair was shown in cutaneous biopsies.[110] But no significant benefit for topical testosterone, dihydrotestosterone, oestrogens and progesterone in the treatment of LS could be demonstrated in randomized controlled trials (see below).

Topical sex hormones

Topical oestrogens. Topical oestrogens are commonly used as a treatment of postmenopausal vulvovaginal atrophy in women.[111,112] However, the postmenopausal vulva shows only minor shrinkage of tissue, and pronounced atrophy should be regarded as suspicious.[113] Topical oestrogens supplemented to the vagina are a well-established treatment in the oestrogen-deficient postmenopausal situation. Oestrogen decrease can cause dryness and splitting of the skin and mucosa resulting in dyspareunia due to decreased vaginal blood flow and less lubrication but is independent from vulval changes of LS, although both conditions may occur simultaneously. Vaginal treatment with topical oestrogens might be of advantage for sexually active postmenopausal women with LS due to its lubrication effect, to avoid soreness and tearing after intercourse. The vulva itself has few oestrogen receptors which however may be upregulated in some situations.[114] Therefore, topical oestrogens for the treatment of LS alone cannot be recommended, even though published data of comparative trials are not available.

Topical testosterone and dihydrotestosterone. Topical testosterone 2% was used in female LS patients and is reported to induce remission of LS in a subgroup of patients, but androgenic side effects like clitoral enlargement, hirsutism, acne vulgaris and amenorrhoea were common and inacceptable.[103–105] Five RCTs are published that compare testosterone with other treatments.[104,115–118] Two small studies did not find significant efficacy of testosterone 2% after 3 months treatment (participant-rated improvement or remission of symptoms/investigator-rated improvement of gross appearance). No significant difference in severe adverse drug reactions was found between the

testosterone and placebo groups.[104,115] A very small cross over trial on dihydrotestosterone versus placebo found no significant efficacy in either participant-rated improvement of symptoms or investigator-rated improvement of gross appearance.[116] One small study found that testosterone was significantly less effective than clobetasol propionate. No significant differences in adverse drug reactions were found between the testosterone and clobetasol propionate groups.[104,119] A very small cross over trial did not find significant differences in efficacy between testosterone and dihydrotestosterone (participant-rated remission of itching; participant-rated remission of dyspareunia; investigator-rated gross improvement).[117] One small study found that testosterone, when used as maintenance therapy after an initial treatment with topical clobetasol propionate, worsened the symptoms ($p < 0.05$) while the vehicle-based placebo caused no change in symptoms or gross appearance.[118] No significant differences in adverse drug reactions between testosterone and placebo were found.[118]

We recommend against the treatment of LS with topical testosterone or dihydrotestosterone.

Topical progesterone. Two case series suggested efficacy of topical progesterone in women with vulval dystrophy.[120,121] A small randomized study for the treatment of 79 LS patients with advanced disease and a mean age of 57 years did not find significant efficacy of progesterone 2% cream when compared to topical clobetasol propionate 0.05% (participant-rated improvement or remission of symptoms/investigator-rated global degree of improvement).[104] Leone et al. investigated 30 patients in an RCT: 15 women were treated topically for 6 months with 2.5% progesterone cream and 15 women were treated with Vaseline. Of the patients treated with progesterone, resolution of symptoms was observed in 9, an improvement in 5 and none worsened. Of the controls, five patients had some benefit, and five worsened. The immunohistochemical scores of pre- and post-treatment biopsies investigated for epidermal growth factor and its receptor were significantly higher after progesterone treatment compared to placebo.[122] There is also a report of the use of 2% progesterone cream in vulval biopsy-proven LS in a child. There was complete resolution of her pruritus. The clinically visible signs of LS persisted.[123] A pilot study suggested that topical progesterone is effective in the treatment of early onset LS in young women when used in a concentration of 8%.[26] In a small randomized controlled trial of 37 premenopausal women with histologically confirmed LS topical progesterone, 8% was compared to topical clobetasol propionate 0.05%.[124] After 12 weeks of treatment, there were no significant differences in patient-administered symptom scores, but physician-evaluated severity score showed significant differences favouring clobetasol propionate. No severe side effects occurred in any of the study groups; however because there was no placebo arm in the study, it is not clear if topical progesterone treatment is completely ineffective.[124]

Nevertheless, topical progesterone has not been shown to be very effective and is not superior to topical clobetasol propionate in the treatment of LS.

We suggest against the use of topical progesterone for the treatment of LS.

Platelet-rich plasma

We **cannot make a recommendation** with respect to platelet rich plasma in women with genital lichen sclerosus.	0	100% agreement (21/21) Evidence- and consensus- based
We **cannot make a recommendation** with respect to platelet rich plasma in girls with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to platelet rich plasma in men with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to platelet rich plasma in boys with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to platelet rich plasma in patients with extragenital lichen sclerosus.	0	

Direct evidence available for:
- Women:
  - 1 non-comparative/non-prospective study ($n = 28$)
  - 1 non-comparative/non-prospective study (adipose-derived mesenchymal cells + platelet-rich plasma) ($n = 15$)
- Females age unknown:
  - 1 non-comparative/non-prospective study ($n = 15$)
  - 1 non-comparative/non-prospective study (adhesiolysis followed by PRP) (n=38)
- Men and boys:
  - 1 non-comparative/non-prospective study ($n = 45$)
- Mixed adults:
  - 1 RCT (AD-SVF+PRP vs. AD-SVF) ($n = 40$)
    - Improvement of symptoms: GRADE ⊗○○○ very low
    - QoL: GRADE ⊗⊗○○ low
  - 1 non-comparative/non-prospective study ($n = 94$)

For specific results, see Evidence report

General introduction to the topic

Platelet-rich plasma (PRP) is an autologous blood-derived product that contains platelet concentrations at least 2/3 times above the normal level and includes platelet related growth factors.[125] The concept of PRP began in the 1970s in the field of haematology to treat patients with thrombocytopenia. In the 1980s and 1990s, PRP began to be used in surgical procedures such as maxillofacial surgery and plastic surgery. Since then, PRP had been used in orthopaedic procedures, cardiac surgery, sports injuries, plastic surgery, gynaecology, urology and more recently in medical aesthetics.[126] Platelets contain α granules that provide various growth factors and cytokines, such as platelet derived growth factors (PDGF), transforming growth factor β1 (TGF β1), TGF β2, vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and epithelial growth factor (EGF),[127] which are important for healing processes by influencing inflammation, angiogenesis, stem cell

migration and cell proliferation.[125,128,129] According to the working definition of PRP, the concentration for PRP must be 1,000,000 platelets/μL,[130] to best stimulate proliferation of endothelial cells and angiogenesis, which in turn has a positive effect on certain diseases.[131]

PRP is produced from the individual's own blood by centrifuging venous blood and removing erythrocytes and platelet poor plasma. There are different systems for the production of PRP (commercially marketed systems or systems developed specifically for experimental studies), resulting in heterogeneous preparations.[132] This affects the comparability of PRP studies.

Mechanisms of action and efficacy

Vulval lichen sclerosus

In a randomized, double-blind, placebo-controlled trial, 19 women received 2 treatments of PRP (5 mL each [subdermally/intradermally] separated by 6 weeks) and 10 received placebo treatments. There was no significant difference in the histopathological evaluation of inflammatory infiltration or in the Clinical Scoring System (CSS) for vulval LS between PRP and placebo.[133]

Fifteen patients treated with the same treatment regimen in an uncontrolled pilot study. In total, 7/12 (58%) patients who completed the trial showed decreased inflammation on their post-treatment biopsies, and 5/12 (42%) had no change or an increase in inflammation. The Investigator's Global Assessment (IGA) indicated a statistically just significant improvement after treatment (pre-treatment: 2.67 ± 0.49 vs. post-treatment 1.83 ± 0.83; $p = 0.0054$). Changes in subjective VAS scores for pruritus and burning were not statistically significant.[134]

A small uncontrolled cohort study of 28 women unresponsive to topical steroids was treated with 3 PRP treatments 4–6 weeks apart and again at 12 months. After the last treatment, no lesion was visible in 8 (29%), in 17 (61%) the lesion was smaller than at the beginning of the therapy and in 3 (11%) there was no change. Fifteen patients (54%) had no more symptoms after treatment.[135]

Penile lichen sclerosus

Forty-five male patients, who failed to improve after at least 6 months of ultrapotent topical steroid therapy or who requested an alternative treatment, were treated with at least two (median 4; range 2–10) PRP treatments (1–3 mL each). The authors described a significant improvement after PRP treatment ($p < 0.001$), both in the IGA on a 6-point Likert scale and in the DLQI (change of IGA 2.04 ± 0.71; change of DLQI 7.73 ± 4.92).[136]

Mixed

In a case series by Tedesco et al., 13 male and 18 female patients with genital LS were treated with 2–4 mL of PRP 3 times every 15 days.[137] After 12 months follow-up, an improvement of the symptoms was observed in 19 patients (62%), stability was observed in 11 patients (35%) and worsening of the disease was observed in one patient (3%).[137] In a later study, Tedesco et al. compared the efficacy of PRP in 43 male and 51 female patients with genital LS.[138] Also in this trial, patients received 2–4 mL of PRP 3 times every 15 days. It is unclear whether the patients described in the first trial were also included in this study. In total, 52.1% of the patients were symptom free after PRP therapy, but 14.9% of the patients stated that they were symptom free before the PRP treatment. The number of patients who still suffered from itching, pain and burning after the treatment was significantly reduced in both sexes (women: 80→22%, 33→8%, 37→16%, respectively; men: 37→9%, 19→5%, 23→3%, respectively). A statistically significant reduction in dyspareunia was only observed in men (men 34%→12%; women 37%→31%).[138]

Dosage

There are no dosage standards. In most studies, 2–5 mL of PRP was injected subdermally and intradermally.[133,134,138,139] In most studies, 2–3 treatments were applied at intervals of 2–6 weeks.[133–135,138,139] However, there were also patients who received up to 10 PRP treatments.[136]

In some studies, PRP was activated with $CaCl_2$ or thrombin before injection to stimulate the platelet degranulation.[135,140] In other studies, no prior ex vivo activation took place.

Safety

No adverse reactions were reported except transient discomfort and bruising at the injection sites.[134]

Special considerations

Some studies mention that the injection site was anaesthetised with numbing creams or injections of local anaesthetics before PRP treatment.[135,136,138]

There are some small trials investigating the efficacy of surgical interventions with additional PRP treatment. In a RCT, 40 patients with genital LS (16 females; 24 males) were treated with adipose tissue derived stromal vascular fraction (ADSVF) or with ADSVF-enriched PRP therapy. The combination therapy was not better and in advanced disease even worse.[139] In other uncontrolled cohort studies, patients were treated with adipose-derived mesenchymal cells and PRP or with adhesiolysis followed by PRP.[141,142]

UV therapy

We **suggest** UVA 1 therapy in women with genital lichen sclerosus as a second choice treatment, taking into account carcinogenicity and practicality.	↑	>75% agreement  (14/15)[1] Evidence- and consensus- based
We **recommend against** UV therapy in girls with genital lichen sclerosus.	↓↓	
We **cannot make a recommendation** with respect to UV therapy in men with genital lichen sclerosus.	0	
We **recommend against** UV therapy in boys with genital lichen sclerosus.	↓↓	
We **recommend** UV therapy in patients with extragenital lichen sclerosus.	↑↑	

[1]1 Abstention

Direct evidence available for:
- Women:
  - 1 RCT (UVA-1)
    - Improvement of symptoms: GRADE ⊗⊗○○ low- ⊗○○○ very low
    - QoL: GRADE ⊗⊗○○ low
    - Physician global assessment: GRADE ⊗○○○ very low
- Extragenital:
  - 2 non-comparative/non-prospective studies (UVA-1) (*n* = 20)
- Mixed (genital and extragenital involvement):
  - 1 non-comparative/non-prospective study (UVA-1) (*n* = 14)

For specific results, see Evidence report

Mechanisms of action and efficacy

Phototherapy, especially with ultraviolet (UV) A, is an effective and well-established treatment option for sclerosing skin diseases such as morphoea and extragenital LS, and numerous studies (including prospective controlled trials) have been performed for both conditions.[143–147] In contrast, only few data exist on the efficacy of UV therapy for genital LS, and most reports are based on small case series or single case reports. In an open pilot study including 12 patients with anogenital inflammatory diseases (including genital LS, genital lichen planus and vulval eczema), cream psoralen plus UVA (PUVA) chemophototherapy resulted in a significant clinical improvement (reduction in size of lesions, erythema and/or pruritus; 10–20 treatments in most patients).[148] In 2006, the first case series of genital LS treated with UVA1 phototherapy was published. All patients were women with severe genital LS uncontrolled by ultrapotent topical corticosteroids. Three patients had moderate and two had minimal clinical improvement, and one of these relapsed within 3 months and another after a year. Both had a further course of UVA1 therapy, resulting in minimal improvement in one and moderate improvement in the other. In the remaining three, disease severity had improved to a point where intermittent use of topical corticosteroids resulted in acceptable control.[149]

In a randomized controlled study comparing the efficacy of UVA1 phototherapy (applied in a special UVA1 device) with high-potent topical corticosteroids (0.05% clobetasol propionate) in 30 women with genital LS, UVA1 resulted in a significant clinical improvement but was inferior to topical high-potent corticosteroids with respect to practicability, relief of itch and improvement in quality of life. The predominantly reported short-term adverse effects of UVA1 phototherapy in this study were mild and included erythema, pruritus, xerosis cutis and tanning.[150]

Dosage

Low (20 J/cm^2) or medium (50 J/cm^2) dose UVA1 phototherapy for a total of 40 applications per cycle.

Safety

In general, UVA1 is well-tolerated, side effects might include early erythema directly after irradiation, tanning of the irradiated lesion as well as itching or burning shortly after treatment.

Monitoring

If possible, clinical examination during UVA1 should be performed weekly or every 14 days.

Special considerations

UVA1 phototherapy can be combined with topical corticosteroids or topical calcipotriol (2 h before or after irradiation).

UVA1 is less potent than topical high-potent corticosteroids in supressing signs and symptoms of genital LS. UVA1 might be considered as alternative therapy for genital LS in cases that failed to respond to other treatments.

UV light in extragenital lichen sclerosus

Only few studies exist on the safety and efficacy of UV light in extragenital LS.[151–153] However, the efficiency of UVA1 phototherapy in extragenital LS was first established by Kreuter et al. in 2001.[152] The authors report improvement of LS lesions following 40 sessions of long-wave UVA1 irradiation (four sessions per week for 10 weeks, total of 40 treatments, 20 J/cm^2 low-dose UVA1 per session, 800 J/cm^2 cumulative dose). One year later, Kreuter et al. were able to present the improvement of extragenital LS in 10 patients, all being treated by the established standard irradiation protocol.[153,154]

As far as PUVA therapy in extragenital LS is concerned, one case report demonstrated a promising therapeutic attempt.[155] Interestingly, single UVA1 progressed from 0.3 to 2.3 J/cm^2 resulting in a cumulative dose of 31.7 J/cm^2 during a 6-week period.

Narrowband (NB)-UV-B phototherapy alone or in combination with salt water (balneophototherapy) is a

well-established therapy for psoriasis. Similar to UVA1, only few case reports exist on NB-UVB for extragenital LS.[151,156] However, a large RCT in patients with morphoea has shown that NB-UV-B significantly improved skin lesions, but medium-dose UVA1 was significantly more effective than NB-UV-B.[157] Based on these findings, NB-UV-B might be considered as an alternative treatment for extragenital LS in centres where UVA1 is not available.

Care has to be taken in patients who may have additional connective tissue diseases, such as lupus erythematosus, which may pose a contraindication for light treatment.[158]

Photodynamic therapy

We cannot make a recommendation with respect to photodynamic therapy in women with genital lichen sclerosus. (off label)	0	>75% agreement  (14/15)[1] Evidence- and consensus- based
We recommend against photodynamic therapy in girls with genital lichen sclerosus.	↓↓	
We cannot make a recommendation with respect to photodynamic therapy in men with genital lichen sclerosus. (off label)	0	
We recommend against photodynamic therapy in boys with genital lichen sclerosus.	↓↓	
We cannot make a recommendation with respect to photodynamic therapy in patients with extragenital lichen sclerosus. (off label)	0	

[1]1 Abstention

Direct evidence available for:
- Women:
  - 1 RCT (ALA-PDT)
    - Improvement of symptoms: GRADE ⊗⊗○○ low
  - 11 non-comparative/non-prospective studies (ALA-PDT) (*n* = 423)

For specific results, see Evidence report

Mechanisms of action and efficacy

In contrast to UV therapy, robust data exist on the use of photodynamic therapy (PDT) in vulval LS. A recently published review of the literature on PDT for genital LS included 11 prospective studies, 5 case series and 4 case reports.[159] Only one controlled cohort study exists.[160] The number of patients in all studies on PDT for vulval LS ranged from 1 to 102. 5-aminolevulinate (5-ALA) was used as the photosensitizer in the majority of studies ($n = 17$), and 19 reports used red light (one report used green light) as light source. In 16 studies, resolution of pruritus, which causes major discomfort for patients with vulval LS, was reported. Besides subjective symptoms, Li et al. reported a significant reduction of objective LS findings including leucoplakia, erythema, hyperkeratosis, purpuric lesions and itching related excoriations.[161] However, other studies found no objective improvement following PDT.[162,163]

Dosage

In most studies, 20% 5-ALA was applied for 4–6 h (mostly 3 h), followed by coherent (630 nm) or non-coherent (570–670 nm) red light. Doses might fluctuate between 9 and 180 J/cm^2, with a range of 100–150 J/cm^2 in most studies. For light intensity, a minimum of 40 and a maximum of 700 mW/cm^2 can be applied. Three to five PDT procedures might be necessary.

Safety

The overall tolerability (pruritus and mild pain in most cases) of PDT in vulval LS was good, and none of the studies were discontinued due to complications. PDT treatments may be repeated several times, with no risk for development of resistance.

Special considerations

PDT is a valuable therapeutic option for vulval LS refractory to standard treatment with high-potent topical corticosteroids. PDT is particularly effective in terms of resolution of subjective symptoms, for example, pruritus.

Laser therapy

We **cannot make a recommendation** for fractionated ablative CO_2 laser treatment in women with genital lichen sclerosus.	0	100% agreement (15/15) Evidence- and consensus- based
We **cannot make a recommendation** for non-ablative Nd:YAG laser in women with genital lichen sclerosus in order to soften the tissue.	0	
We **cannot make a recommendation** for ablative CO_2 laser treatment in men with genital lichen sclerosus.	0	
We **cannot make a recommendation** for non-ablative Nd:YAG laser in men with genital lichen sclerosus in order to soften the tissue.	0	
We **cannot make a recommendation** with respect to laser treatment in patients with extragenital lichen sclerosus.	0	
We **cannot make a recommendation** for combination laser treatment in patients with lichen sclerosus (e.g. ablative and non-ablative).	0	
We **recommend against** using laser treatment in children with lichen sclerosus.	↓↓	

Direct evidence available for:

- Women:
  - 2 RCTs (CO_2 laser)
    - Improvement of symptoms: GRADE ⊗⊗○○ low - ⊗○○○ very low
    - QoL: GRADE ⊗⊗⊗○ moderate
    - Sexual function: GRADE ⊗○○○ very low
    - Urinary function: GRADE ⊗⊗○○ low
    - Patient global assessment: GRADE ⊗⊗○○ low - ⊗○○○ very low
    - Physician global assessment: GRADE ⊗⊗○○ low
    - Minor adverse events: GRADE ⊗○○○ very low
  - 1 RCT (Nd:YAG laser)
    - Improvement of symptoms: GRADE ⊗⊗○○ low - ⊗○○○ very low
    - Patient global assessment: GRADE ⊗⊗○○low
    - Physician global assessment: GRADE ⊗○○○ very low
  - 6 non-comparative/non-prospective studies (CO_2 laser) (n = 159)
  - 1 non-comparative/non-prospective study (Er:YAG laser) (n = 28)
- Females age unclear:
  - 1 non-comparative/non-prospective study (CO_2 laser) (n = 42)
- Men:
  - 2 non-comparative/non-prospective studies (CO_2 laser) (n = 72)
- Mixed adults:
  - 1 non-comparative/non-prospective study (CO_2 laser) (n = 10)

For specific results, see Evidence Report

General introduction to laser treatment in lichen sclerosus

Laser therapy has recently been suggested as a new treatment option for genital LS. Recommendations are based on a few studies including mostly women.

Patients should be aware of commercial practices highlighting the efficacy of laser therapy in genital LS. Before performing laser therapy, patients should carefully discuss such treatment with a practitioner (dermatologist, gynaecologist, urologist) specialized in the management of LS.

Various lasers are in use. **Fractionated CO_2 laser** has got a wavelength of 10,600 nm allowing a superficial microablative effect in soft tissues. The ablative CO_2 laser may reduce hyperkeratoses, but will not suppress the inflammatory process and should therefore be used in combination with topical steroids. It is especially useful in hyperkeratotic disease.

(Ongoing studies NCT05010421, NCT04951206, NCT05243563, NCT03665584).

Nd:YAG laser, 1064 nm wavelength, has an adequate penetration depth (5 mm) to induce a heat response in the dermis without ablative change. It is thought to reduce inflammation and remodel collagen, and possibly softens sclerosis and reduces fissuring. It is not known if, for example, during and after Nd:YAG laser treatment topical anti-inflammatory treatment will be needed.

By variation of pulse settings, the **Er:YAG laser** with a wavelength of 2940 nm can be used in an ablative or a non-ablative mode. Non-ablative settings have an adequate penetration depth to induce a heat response in the dermis, and ablative settings enable the peeling of the skin surface.

The combination of Er:YAG and Nd:YAG lasers allows superficial ablation plus regeneration of the deep connective tissue (ongoing study NCT03926299).

A systematic review for laser treatment in genital LS discusses 24 studies, including 6 RCTs.[164] Diode laser, non-ablative Nd:YAG laser and fractionated CO_2 laser were used. Unfortunately, results were highly heterogeneous, and the methodological quality was very low. Therefore, no meta-analysis could be performed. The authors conclude that there is not enough high-quality evidence to recommend laser treatment for genital LS and that long-term data over 6 months are missing.

Carbon dioxide (CO_2) laser

Efficacy

In a prospective, randomized, double-blind and placebo-controlled study comparing 19 women treated with fractionated CO_2 laser and 18 women with a sham laser, no significant improvement in the histopathological change of vulval LS with fractionated CO_2 laser therapy compared with sham treatment (95% CI −1.14, 1.06, p = 0.76) was found, indicating that fractionated CO_2 laser is not an effective monotherapy for genital LS.[165] A large placebo effect has been observed since women in both the active treatment arm and sham treatment arm experienced a statistically significant improvement in symptoms, highlighting the importance of randomized controlled trials.

Two studies analysed the efficacy of the CO_2 laser treatment in men and women with no other disease than LS.[166,167] In a retrospective study of 62 men, Windahl showed that after a median follow-up of 14 years, 80% of the patients had neither symptoms nor signs of LS.[166] However, no control group or histopathological evaluation was available. Kartamaa et al.

retrospectively concluded the efficacy of the CO_2 laser for skin lesions in a small number of patients, five men and five women. Skin lesions improved but reoccurred in some patients.[167]

Results are conflicting, and potential confounders have to be considered: (a) there is a known positive effect of the fractionated laser treatment on the genitourinary syndrome of menopause (GSM). Therefore, because of potential overlap of symptoms in some studies it may be difficult to clearly distinguish if the treatment effect is improving GSM or LS symptoms; (b) in some studies, topical steroids were continued during laser treatment and (c) methodological quality was poor.[166,167] In summary, a beneficial effect of the CO_2 laser on clinical symptoms in women with genital atrophy (GSM) can be assumed; however, a direct effect on the lichenoid inflammatory reaction of LS is at this point questionable.

Safety

CO_2 laser treatment of genital LS was mostly well tolerated.[168,169] Before treatment, numbing of the skin is always needed.

Balchander et al. described a burning pain lasting for more than 7 days in 2 out of 40 women.[170] Minor burning and blistering at the laser site has also been observed by Burkett et al.[171]

Ongoing trials

NCT03665584: The purpose of this study is to look at the efficacy and safety of the $FxCO_2$ laser treatment (laser energy emitted) for LS as compared to a sham treatment (very minimal laser energy emitted).

NCT05010421: In this prospective, randomized, open-label, comparative study, treatment success after three courses of non-ablative treatment with CO_2 laser every 14 days will be compared with treatment success after topical application of clobetasol 0.05% over 3 months (daily in the first month, every other day in month 2 and 3 times/week during month 3) at the time point 3 months after treatment initiation.

Neodymium:yttrium aluminium garnet (Nd:YAG) and Erbium:yttrium aluminium garnet (Er:YAG) lasers

Efficacy

In a randomized, non-blinded study comparing 20 women using both topical steroids plus 3 non-ablative Nd:YAG laser sessions to 20 women using topical steroids alone, Bizjak-Ogrinc et al. showed no statistical difference in inflammation between the two groups comparing pre-treatment and post-treatment biopsies.[172] Symptoms including itch, burning and pain rated on a visual analogue scale were reduced in both groups compared with baseline but they were statistically significantly better in the laser group at one and 3 months follow-up and the effect was still significant at 6 months, although these symptoms started to increase again.

A non-controlled study of 28 women treated with Er:YAG laser showed a statistically significant reduction of itching and pain (pre- vs. post-treatment) but no change in dyspareunia and hyperkeratosis.[173] A control group or histopathological evaluation of the effect was not available.

Safety

Nd:YAG laser treatment for genital LS was well tolerated. Numbing of the skin is not necessarily needed. Some patients reported minimal discomfort described as a sensation of warmth in the study of Bizjak-Ogrinc et al.[172] In the study of Gomez Frieiro et al. 7% of the women considered the treatment by Er:YAG as tolerable.[173]

Ongoing trials

NCT03926299: The aim of this study is to test a new, minimally invasive dual laser technique to treat vulval LS. Efficacy and safety of the thermal non-ablative Nd:YAG laser and the ablative Er:YAG laser (FotonaSmooth SP® Spectro laser device) is determined and compared to the current standard treatment with high-dose topical steroids. The hypothesis is that laser therapy is effective and similar to standard steroid therapy. Results are expected in 2023.

Cryotherapy

We **cannot make a recommendation** with respect to cryotherapy in women with genital lichen sclerosus.	0	100% agreement (21/21) Evidence- and consensus- based
We **cannot make a recommendation** with respect to cryotherapy in girls with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to cryotherapy in men with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to cryotherapy in boys with genital lichen sclerosus.	0	
We **cannot make a recommendation** with respect to cryotherapy in patients with extragenital lichen sclerosus.	0	
Direct evidence available for: • Women and girls: ○ 1 non-comparative/non-prospective study (n = 31) For specific results, see Evidence report		

Mechanisms of action and efficacy

Cryotherapy, also known as cryosurgery or cryoablation, is a minimally invasive procedure to freeze superficial cutaneous lesions. Liquid nitrogen (temperature – 196°C) is used in most cases as cryogen. Cryotherapy is an easy to perform, inexpensive and highly effective treatment option for a variety of cutaneous diseases, including actinic and seborrheic keratoses, viral warts or keloids.[174] It may be applied as open spray, cryoprobe or close contact technique.[175] No controlled studies exist on the use of cryotherapy for vulval LS. In a retrospective case series of 22 adult and 9 juvenile patients with vulval LS, all patients experienced a significant clinical improvement of skin lesions and symptoms, especially in pruritus.[176]

Dosage

Based on the current lack of robust data, cryotherapy cannot be recommended as a first or second line treatment for vulval LS. However, in experienced hands cryotherapy may be considered (1 cycle for 4–8 s on an area of about 4 square centimetres, excluding the clitoris, preferably in open spray or cryoprobe technique after application of topical *anaesthetic* agents) as a treatment option in patients with unbearable pruritus in whom guideline-conform treatment has failed.

Safety

Patients have to be informed about side effects of cryotherapy, which include blistering of the skin and pain.

Systemic treatment

We **suggest** acitretin, taking into account teratogenicity, if systemic therapy is needed in women with genital lichen sclerosus. (off label)	↑	>75% agreement (17/18)[1] Evidence- and consensus- based
We **suggest** acitretin if systemic therapy is needed in men with genital lichen sclerosus. (off label)	↑	>75% agreement (15/17)[2] Evidence- and consensus- based
We **suggest** MTX, taking into account teratogenicity, if systemic treatment is needed in adult patients with genital and/or extragenital lichen sclerosus. (off label)	↑	>75% agreement (15/16)[1] Expert Consensus
We **recommend against** potassium para-aminobenzoate as a treatment for lichen sclerosus.	↓↓	100% agreement (15/15) Evidence- and consensus- based

[1]1 Abstention

[2]2 Abstention

Direct evidence available for:
- Women:
  - 1 RCT (acitretin)
    - Improvement of symptoms: GRADE ⊗⊗⊗○ moderate
    - Patient global assessment: GRADE ⊗⊗⊗○moderate
    - Minor adverse events: GRADE ⊗⊗⊗⊗ high
- Men:
  - 1 RCT (acitretin)
    - Improvement of symptoms: GRADE ⊗⊗⊗○ moderate
    - QoL: GRADE ⊗⊗⊗○moderate
    - Physician global assessment: GRADE ⊗⊗⊗⊗ high
- Mixed adults:
  - 1 RCT (paraminobenzote)
    - Improvement of symptoms: GRADE ⊗○○○ very low
- Extragenital LS:
  - 1 non-comparative/non-prospective study (MTX) (n = 24)

For specific results, see Evidence report

Introduction

Many systemic treatments have been tried to improve LS. These include glucocorticosteroids; oral retinoids; ciclosporin; methotrexate; hydroxycarbamide, an antineoplastic drug used in myeloproliferative disorders; cycloferon, a low molecular weight interferon inducing substance; fumarate, used in the treatment of plaque psoriasis; hydroxychloroquine an antimalarial drug, used to reduce inflammation in the treatment of, for example, rheumatoid arthritis and lupus erythematosus; antibiotics (penicillins, cephalosporins, dirithromycin, doxycycline, etc.); sulfasalazine, a sulfa drug and derivative of mesalazine, used in the treatment of inflammatory bowel disease and rheumatoid arthritis; Vitamin D, 1,25-dihydroxyvitamin D, the biologically active, hormonal form of the nutrient is important in the metabolism of calcium and phosphorus and is critical in building and maintaining healthy bones; Vitamin A & E, Vitamin A plays a role in regulating epithelial proliferation and differentiation, there are anti-oxidant effects of Vitamin E; potassium para-aminobenzoate, PABA is an intermediate in the bacterial synthesis of folate (Vitamin B11) and is structurally similar to Sulfonamide drugs. The potassium salt is used as a drug against fibrotic skin disorders.[47] Biologics were recently tried in single cases, and bigger studies have to show their effect.

The level of evidence is very low, and the drugs are not tried in all forms of LS.

Systemic retinoids

Mechanisms of action and efficacy

There are several case series as well as two RCTs reporting on the treatment of LS with oral retinoids. In an open uncontrolled study, Mørk et al. observed an improvement of clinical symptoms (patients' and physicians' assessment) in six of eight patients with treatment-resistant vulval LS on oral etretinate (1 mg/kg/day) after 14–18 weeks.[177] Romppanen et al. treated 19 women with vulval LS with oral etretinate for 3 months (initial dose 0.54 mg/kg/day and maintenance dose 0.26 mg/kg/day).[178] A decrease in severity was achieved in nearly all cases among the group with severe vulval dystrophy.[178] Furthermore, two small double-blind, placebo-controlled studies for the treatment of genital LS with acitretin are published.[179,180] In a multicentre, double-blind study, Bousema et al. treated patients (78 enrolled, 46 included in efficacy analysis) with vulval LS with 20–30 mg acitretin or placebo for a total of 16 weeks. Symptoms and signs improved in the treatment group as well as in the placebo group. However, intensity of all symptoms and signs was lower in the acitretin group, with a statistically significant difference for pruritus, atrophy and hyperkeratosis.[179] In another RCT by Ioannides et al., 52 male patients with severe, long-standing LS were randomized in a 2:1 ratio to receive acitretin (35 mg) or placebo for 20 weeks. Mean total clinical score of the acitretin group was significantly lower

than that of the controls, which was also accompanied by a significant improvement in mean DLQI.[180] Based on these results, the authors concluded that acitretin is effective in longstanding male LS.[179]

Safety

Retinoids are usually well tolerated, but sicca symptoms often occur as a side effect. Cholesterol, triglycerides and liver enzyme levels can increase during therapy, and should be checked regularly before and during therapy. Systemic retinoids are highly teratogenic; therefore, all women of childbearing age must use safe contraception (during therapy and, depending on the drug, for up to 3 years after cessation of therapy).

Special considerations

Retinoids may be considered if standard therapy for LS has failed.

Methotrexate

Mechanisms of action and efficacy

Methotrexate (MTX) is an antimetabolite and antifolate drug and acts by inhibiting the metabolism of folic acid. It is used in treatment of cancer and autoimmune diseases. A retrospective case series described 28 patients with LS, (24/28 with extragenital involvement) who were treated with MTX 2.5–17.5 mg weekly. There was initial improvement of LS in 21/28 cases and sustained improvement in 15 cases. Most patients were treated in combination with topical steroids or tacrolimus.[181] In another trial, seven patients with generalized LS (5 genital plus skin; 2 only skin) were treated with high-dose intravenous methylprednisolone sodium succinate, given as a 1000 mg single dose for 3 consecutive days monthly plus MTX 15 mg/week (oral) for at least 6 months (max. 10 months). All were previously unsuccessfully treated with topical steroids and UV phototherapy. Cutaneous LS in all patients improved after usually 3 months of treatment; 100% cure was not achieved, and the effect on genital lesions was not reported. Adverse effects observed (nausea in 3 patients, headache in 3 and a 2-fold increase of liver enzyme levels in 1) were moderate and disappeared after the end of treatment.[182] A patient with generalized LS involving the skin and anogenital site was successfully treated with MTX 10 mg/week for 8 months; improvement was noticed by 3 weeks and excellent response after 5 months.[183]

Dosage

MTX between 10 and 15 mg/week (subcutaneous or oral) for 6 months possibly combined with systemic steroids is reported to improve treatment-resistant generalized LS.

Safety

The most common side effects are gastrointestinal problems, headache, fatigue, mood changes[184] and elevated liver enzymes. Pancytopenias occur mainly in overdoses. Idiopathic pulmonary fibrosis has rarely been reported. Before starting MTX therapy, chronic infections (e.g., hepatitis B/C, HIV and tuberculosis) must be excluded. Complete blood count, kidney and liver profile are mandatory before and regularly during therapy. National guidelines should be consulted.

Special considerations

Taking 5 mg of folic acid per week on a 'non-MTX day', for example, 24 h after the administration of MTX, may reduce haematological side effects. Women and men must use safe contraception during therapy and for 6 months after therapy.

There is hardly any report regarding the effect of MTX in genital LS. In a few reports of extragenital LS treated with MTX, MTX is mentioned to be effective in genital LS next to extragenital disease. Therefore, MTX may be tried if standard treatment fails in extragenital as well as genital LS.

Potassium para-aminobenzoate

Mechanisms of action and efficacy

PABA is an intermediate in the bacterial synthesis of folate (Vitamin B11) and is structurally similar to sulfonamide drugs. The potassium salt is used as a drug against fibrotic skin disorders.

A double-blind placebo-controlled trial of oral para-aminobenzoate (Potaba) was carried out with 25 patients suffering from genital and extragenital LS. Potaba 3 g capsules four times daily versus placebo was tested in a RCT. Of the 21 patients who completed the 2-month trial, six showed some improvement on Potaba against seven on the placebo, an insignificant difference. Adverse effects were bad taste, vomiting and a rash.[185] Potassium para-aminobenzoate cannot be recommended.

Doxycycline

Mechanisms of action and efficacy

The hints towards Borrelia burgdorferi as a trigger in LS are impressive and accumulating but remain conflicting. There are few reports about antibiotic treatment in LS; however, doxycycline, penicillins and cephalosporines were successfully used[186–188]; this warrants further study.

There are hardly any studies on the effect of doxycycline in LS; however, if standard treatment with topical steroids fails, doxycycline may be tried.

Other therapeutic approaches. There are initial considerations and first case reports of treatment with biologics. A case of extragenital LS with itch and lichenification responded to dupilumab[189] and a case of ankylosing spondylitis and extragenital LS responded to secukinumab.[190] Two case reports described two patients with penile LS treated with intralesional adalimumab

40 mg/mL either twice weekly for 3 months (then every 6 weeks for 8 months) or once every 2 weeks for 8 weeks.[191,192] Both patients achieved significant improvement, with one patient experiencing complete relief of urinary symptoms after four biweekly injections and later complete response after transitioning to subcutaneous administration of adalimumab. The other patient achieved near complete response after 4 weeks, which was sustained for 8 months until a 10-week gap in treatment resulted in relapse. The patient was thereafter continued on biweekly injections with maintenance of mild disease. No side effects were reported.[193]

Surgical interventions

We **suggest** de-adhesion / synechiolysis / perineoplasty in women with lichen sclerosus who have a persistent introital stenosis that causes mechanical problems in voiding or sexual intercourse, despite guideline-conform treatment with steroids.	↑	>75% agreement  (14/17)[1] Expert Consensus
We **recommend against** surgical treatment for management of genital lichen sclerosus in girls.	↓↓	>75% agreement  (17/18) Expert Consensus
We **suggest** circumcision, preferably removing the complete foreskin if guideline-conform treatment with e.g. steroids in men with phimosis caused by lichen sclerosus fails.	↑	100% agreement  (16/16) Expert Consensus
We **suggest** frenuloplasty in combination with intralesional triamcinolone or alternatively, a complete circumcision if guideline-conform treatment with e.g. steroids in men with scarring or shortening of the frenulum caused by lichen sclerosus fails.	↑	100% agreement  (13/13) Expert Consensus
We **suggest** urethroplasty using oral mucosa grafts in men with urethral stricture due to lichen sclerosus causing mechanical problems in voiding or sexual intercourse.	↑	>75% agreement  (12/15)[2] Expert Consensus
We **suggest** circumcision, preferably removing the complete foreskin if guideline-conform treatment with e.g. steroids in boys with phimosis caused by lichen sclerosus fails.	↑	100% agreement  (15/15) Expert Consensus
We **suggest** frenuloplasty in combination with intralesional triamcinolone, or alternatively, a complete circumcision if guideline-conform treatment with e.g. steroids fails in boys with scarring or shortening of the frenulum caused by lichen sclerosus.	↑	>75% agreement  (13/15)[1] Expert Consensus

[1]2 Abstention

[2]3 Abstention

Prior to surgery in females we **recommend** • that women are informed about and agree to the continuation of topical treatment after surgery, usually with topical steroids. • interdisciplinary counselling including specialized pelvic floor physiotherapists and sex therapists. For surgical procedures in males we **recommend** • removing the complete foreskin. • having the removed foreskin investigated by a histopathologist to confirm lichen sclerosus and to exclude precancerous lesions like severe dysplasia, requiring a close follow-up after surgery. • pre- and post-operative treatment with topical corticosteroid ointments, e.g. 4 weeks before and 4-12 weeks after the procedure, starting 1 week postoperatively.	↑↑	>75% agreement  (14/15)[1] Expert Consensus

[1]1 Abstention

Surgical interventions in females

Vulval LS can at any age cause scarring of the genitalia including agglutination of the labia minora, phimosis of the clitoral hood and narrowing of the introitus[43,194–196] leading to a decreased quality of life including sexuality and voiding problems. Surgical interventions in females with LS are indicated to improve urinary and sexual function, quality of life, treat precancerous lesions or vulval cancer. Treatment of LS associated vulval cancer will not be discussed in this guideline.

Women with vulval LS have a significantly decreased Female Genital Self-Image Scale (FGSIS), which correlates with sexual function.[197] Brauer et al. investigated the motives of women with LS undergoing surgery.[16] The main motives were the desire to be a 'normal' woman, the desire to sexually satisfy the male partner, and the desire to regain the experience of intimacy and sexual enjoyment.[198] However, Lauber et al. observed a high number of patients with recurrent LS activity after surgery (56.1%); this may be triggered by increased sexual activity after surgery or surgery itself.[199] Also, Rangatchew et al. describe an increase in dyspareunia/apareunia after surgery in sexually active women as a result of LS relapse.[200]

Furthermore, several other factors affect women's sexual life apart from LS, such as pelvic floor and vaginal spasms, lower urinary tract symptoms (LUTS) and psychological aspects. Some of the patients also report sensory symptoms, which might not only be due to scarring, but driven by damage of small nerve fibres during the course of LS.[201]

Interdisciplinary counselling including specialized pelvic floor physiotherapists and sex therapists prior to surgery is crucial. Surgery requires a strict protocol of perioperative treatment, including good local care and pre- and postoperative application of topical steroids until the wounds are healed. Prior to surgery, the motivation for vulval surgery and the expectations regarding the surgical outcome need to be clarified and discussed in order to achieve treatment satisfaction. Surgical treatment should be reserved for symptomatic patients suffering, for example, from recurrent tearing during intercourse (vulval granuloma fissuratum), phimosis with possibly decreased clitoral sensation and stenosis of the introitus or urethral opening.

All these factors need to be discussed prior to surgery, and patients need to be carefully selected in order to have a good chance for the desired outcome after surgery. Furthermore, after the surgery the recommended treatment for LS (anti-inflammatory treatment, emollients) has to be continued long-term.

Women with LS very often suffer from lower urinary tract symptoms (LUTS), including abacterial cystitis. Urethral strictures due to LS are hardly observed in women and surgical intervention for this problem in females is sparsely described.[202]

Perineoplasty (modified Fenton's procedure), during which the posterior fourchette is excised and replaced by a tension-free vaginal advancement flap, was shown to be a safe procedure in these patients, with a low complication and a high satisfaction rate.[203–207]

Perineoplasty provides good functional results, enabling patients to resume or regain painless vaginal intercourse with a high satisfaction rate and low complication rate. In a long-term survey of 41 patients who underwent perineoplasty and de-adhesion, the overall satisfaction rate improved over time (90% after at least 6 months), suggesting good long-term results in compliant patients.[199] However, in this study patients underwent surgery to improve their sexual life, but 31.7% of patients were postoperatively not sexually active. There are no randomized studies available in this setting, so it can be assumed that studies are performed in highly selected patients. More recent studies report that surgery improved the sexual life in most patients; however, most patients still had pain during intercourse.[199,200,206,208,209] In most studies, patients were treated perioperatively with topical steroids. In case the perineoplasty procedure is not successful or as an alternative approach, Frapell et al. suggest a double opposing Z-plasty with VY advancement of the perineum (Plymouth procedure).[210]

Other surgical treatments are the lysis of the labial fusion, de-hooding of the clitoral glans in case of phimosis (de-adhesion) and anterior vestibuloplasty with vaginal epithelium grafts.[199,205,206,208]

Surgical interventions in males

If the standard anti-inflammatory treatment of LS in males does not lead to the desired result, surgery may be an option.

There is no surgical gold standard for the treatment of male genital LS. All recommendations have been based on nonrandomized studies and expert opinion.[211]

Indications for surgery in males with LS are as follows:

- Phimosis
- Sclerosis of the frenulum
- Lesions of the glans (expecting that they may improve after removal of the foreskin)
- Urethral strictures
- Cancerous or precancerous lesions

Circumcision for phimosis and changes of the glans

- Complete removal of the foreskin is recommended
- The removed foreskin should be sent for histological investigation to confirm LS and to exclude precancerous lesions like severe dysplasia or carcinomas, requiring a close follow-up after surgery.
- During circumcision, it is mandatory to carefully evaluate and calibrate the external urethral meatus and navicular urethra (e.g., using progressive Nelaton plastic catheters from 10 to 16 Charrière).
- Potential adverse effects must be explained to the patient:
  - Bleeding,
  - Infection,
  - Meatal stenosis,
  - Loss of sensibility of the penile skin and/or
  - Fistulae of the urethra after circumcision are rare, even in case of LS surgery;
  - Psychological problems (rare)
  - Circumcision in general bears the risk of meatal stenosis (around 1%), mainly seen in boys (because of the small lumen), but in cases of LS it is tenfold higher (10%). The reason could be the inflammatory process of the perifrenular area.
- In obese patients with LS, the 'environment' has to be restored. Occlusive effects of a 'fat apron' need to be avoided and repaired if possible.
- Circumcision offers the highest rate of cure, but if the foreskin is preserved, preputioplasty and intralesional triamcinolone may be offered.

Urethral strictures

The involvement of the urethra in LS is well known. Often the anterior male urethra (meatus, navicular, penile and bulbar tracts) is affected in genital LS,[212–214] however, also other parts of the urethra may be affected.[215] LS patients presenting with obstructive or irritative urinary symptoms are requested to have uroflowmetry and retrograde and voiding urethrography performed to determine if and where LS affects the urethra.

The surgical interventions for LS urethral stricture repair are related to the site and extension of the disease.

1. Strictures involving the external urinary meatus and navicular urethra are managed by:

(A). Wide meatotomy.
(B). One-stage meatoplasty using oral mucosa transplant.
(C). Two-stage meatoplasty using oral mucosa transplant.

2. Strictures involving the penile urethra are managed by:
(A). First-stage urethroplasty (Johanson procedure).
(B). One-stage urethroplasty using oral mucosa transplant.[216]
(C). Two-stage urethroplasty using oral mucosa transplant.
3. Strictures involving the penile and bulbar urethra (panurethral stricture) are managed by:
(A). One-stage urethroplasty using two oral mucosa grafts transplant.[217]
(B). Definitive urinary diversion by perineal urethrostomy.[47,218,219]

It is very difficult to provide definite advice regarding the technique of choice, there are no randomized studies. The surgical technique should be based on the following parameters:

- Site, extension and pathological involvement of the urethra by LS.
- Surgical background and preference of the surgeon.
- Patient's counselling and acceptance of the surgeon's choice.

All these procedures are highly specialized and should only be performed by experienced surgeons. Potential adverse effects include[220]:

- Development of fistula
- Urinary tract infection
- Strictures

Surgical intervention in boys

Circumcision

A recent review showed that topical corticosteroids in boys prevent circumcision in up to 35% of cases.[221] Median follow-up time, however, was short (median 4 months, range 6 weeks to 5 years). LS is thought to rarely occur in circumcised males[222] and circumcision is thought to have a high cure rate, but good studies are missing.

However, there are several studies which point out the curative effect of complete circumcision in boys. In a prospective study, 10 boys with LS were clinically controlled 5 years after surgery and showed no signs of recurrence.[5] This observation was confirmed in a much greater prospective series of 471 LS cases. In total, 471 boys were followed up to for 12 months postoperatively, then yearly (no information about the mean follow-up time and the reason why half of the patients were lost to follow-up). At 1 year follow-up, all patients were still in remission; the lesions of the glans disappeared within 6 months in 229 boys, in the remaining boys thereafter. The more severe the lesions are, the later they usually resolve, for example, in the second year post-surgery.[223]

A couple of studies point out the necessity of complete removal of the foreskin to prevent recurrence. One retrospective series of 225 LS cases report 5 recurrences (50%) out of 10 LS cases treated by partial circumcision.[224]

Adverse effects

In boys with LS, meatal stenosis, urethral strictures and phimosis may be observed during the surgical procedure. Cohort studies show that 7%–20% of boys circumcised for LS subsequently need a meatal procedure in the form of a meatotomy or meatoplasty within weeks to several months after circumcision.[225] However, a second operation only weeks after circumcision bears a high risk of recurrence; it should only be performed several months later, once LS is in remission.[224] Homer et al. showed that boys with LS requiring meatal procedures (meatal dilation in 25, meatotomy in 24) rarely underwent a meatal procedure at circumcision (4 of 49) and were less likely to have received preoperative topical steroids compared to boys not needing a later meatal procedure (2 of 49 vs. 49 of 151, $p < 0.05$).[226] Therefore, males with LS should be carefully investigated preoperatively and all features of LS should be operated on in the same procedure; furthermore, postoperative treatment with a potent topical steroid may reduce the rate of meatal stenoses (from 10% to 5%).

Wilkinson showed the successful combination of preputioplasty and intraoperative injection of triamcinolone into the LS lesions in 84 out of 104 cases.[227] Eighty-four of 104 (81%) in the preputioplasty group had a fully retractile foreskin and no macroscopic evidence of LS. Of 104, 14 (13%) developed recurrent symptoms/LS requiring circumcision or repeat foreskin preputioplasty.[227] Lansdale et al. compared preputioplasty and intralesional triamcinolone (PIT) and circumcision in an RCT. However, due to small numbers of participants the efficacy of the technique could not be judged. There is no information about preoperative treatment.[228]

Recurrence after complete circumcision is reported particularly in cases of obese males with buried (concealed) penis.[224,229–232]

Meatodilatation, meatotomy, meatoplasty

The rate of meatal stenoses is reported in 2%–37% patients with penile LS.[223,232] Meatal stenosis can be part of the initial clinical picture or develop several months after circumcision (as part of LS or as an adverse effect of surgery).

Urethral stenosis in boys

Urethral LS is also seen after surgery for hypospadias in boys. In a descriptive analysis of 1.176 patients with failed hypospadias repair requiring further surgery, 89 (7.6%) had histologically proven LS.[233] Apart from these special circumstances, urethral LS in boys has been reported in only five cases (2 out of 130 LS cases: Barbagli 2004; 3 out of 41 LS cases: Gargollo 2005).[215,232] Both studies collected data

over a period of 10 years. All five patients underwent one or more procedures (circumcision, cystoscopy) before urethral LS developed.

Arena (2018) used uroflowmetry (UF) to assess the outcome of 75 circumcised boys. Circumcision was followed by 3 months of clobetasol propionate 0.05% ointment.[234] At 2 weeks, 32 of 75 patients (42.7%) displayed a pathological UF. At 6 months, 15 patients (20%) had pathological UF and a new cycle of clobetasol was prescribed. At 1 year, 10 patients (13.3%) had pathological UF and underwent progressive urethral dilatation or meatoplasty. At 18 months, 71 patients (94.7%) displayed regular UF, 3 underwent a meatoplasty and 1 a staged urethroplasty for a severe urethral stenosis. At 2 years, UF was normal in 74 out of 75 (98.7%). Therefore, clinical and uroflowmetric follow-up of paediatric patients with LS is mandatory for a prompt identification of post-voiding dysfunction; the application of very potent topical steroids after circumcision in boys seems advantages, and only 13% of patients needed surgical intervention for urethral or meatal stenosis.

Surgical intervention in men

Circumcision

Surgical treatment by circumcision can be curative if the disease is treated early when still localized to prepuce and glans only. Data of 287 men with genital LS were reviewed retrospectively. Complete circumcision led to healing in 276 (92%). Detailed follow-up data is not available; however, the authors state that 'mild glans disease may revert to a normal appearance within 6 months, and in more severe cases resolution may continue for up to 2 years after circumcision'. The disease remained active in 11 (3.9%) patients requiring glans resurfacing or urethroplasty (the study does not differentiate between boys and men). If LS led to a buried corona with a fusion between foreskin and glans, circumcision may be a challenging procedure requiring subtle separation of the adhesions and complete removal of the foreskin (circumcision).[231] Another study of 215 Patients with genital and/or urethral LS reported a 100% cure after circumcision if LS was limited to the foreskin (mean follow-up 65 months, range 12–170 months).[235] Long-term follow-up studies have not been performed.

Glans resurfacing

If LS remains active on the surface of the glans after circumcision, topical treatment seems to be of limited benefit (Garaffa[236] used only 'mild' topical steroids, Depasquale[231] used clobetasol propionate 0.05%). Ongoing LS carries the risk of progressing into the urethra and may lead to severe impairment of sexual and urinary function. Surgical therapy consists in removing the affected skin and replacing it with skin grafts. An alternative technique is laser ablation. Garaffa reported the largest series of patients treated by glans resurfacing, 26 of 31 (84%) operated patients were reported to be 'fully satisfied with cosmetic and functional results'.[236,237] Resurfacing in cases of persistent glanular LS is successful in the majority of patients.

Meatal dilatation, meatotomy, meatoplasty

If meatal stenosis occurs and is strictly limited to the meatal lips meatodilation, meatotomy or meatoplasty may be successful. Meatotomy by a ventral slit followed by dilatation, however, may lead to a distal hypospadia deformity as reported in 6 out of 32 LS patients (20%).[238] Some, therefore, prefer meatoplasty (85% satisfactory results reported).[239] Long-term results (10 years) are 'excellent'.[240,241] Kulkarni reported a success rate of 80% in 15 patients (mean follow-up 59 months, range 12–139 months), but 100% if combined with circumcision (8 patients).[235] If LS spreads to the fossa navicularis, the best surgical strategy to assure a high rate of objective and subjective success is not determined. Dilatation and urethrotomy continue to be the most commonly used approaches despite frequent progression of disease with subsequent need of surgical repair. Dilation and urethrotomy may also increase scar formation, thus adding to stricture length and severity, complicating subsequent open repair.[242] A generous ventral meatotomy followed by anti-inflammatory topical treatment may help.[243] But cosmetic results are unsatisfactory as it may produce a hypospadic meatus and may lead to a splaying micturition. Alternatively, meatoplasty with a dorsal oral mucosa graft is recommended.[243] But both meatotomy and meatoplasty may result in stricture recurrence (20.5% vs. 7.5%, $p = 0.04$).[244] Comparative results of 93 patients who underwent distal urethroplasty for isolated fossa navicularis and meatal strictures including 42% of patients with LS were reported. Successful reconstruction requiring no further intervention occurred in 84% of patients overall. Subgroup analysis revealed success in 87% of men with simple meatotomy, 75% with meatoplasty and 66% of one-stage reconstruction using a substitute material. Patients with LS showed a significantly greater rate of stricture recurrence (20.5% vs. 7.5%, $p = 0.04$). Patients who underwent simple meatotomy were investigated by questionnaire and most (84%) were either satisfied or very satisfied with the results and 82% described their outcomes as good or excellent.[244] The involvement of LS in urethral strictures on pathological examination of tissue of 99 male patients was studied. Authors concluded that genital LS with meatal involvement should be considered as a negative prognostic factor as far as proximal urethral involvement is concerned and patients with meatal stenosis require careful follow-up. It was speculated that urinary obstruction caused by distal, meatal or navicularis stenosis may promote epithelisation of the urethral mucosa, creating the basis for LS to diffuse into the remaining tract.[219]

Snodgrass et al. found that 40% of patients who had circumcision for meatal LS (complete excision, including total replacement of the involved urethra) had recurrences of LS at a median of 2 years.[222] Ten of the 12 investigated patients had hypospadias (8 of them prior to surgery). There was one 10-year-old boy who developed LS after neonatal circumcision (which is regarded to be very rare) and one 6-year-old

boy with meatal involvement after circumcision for LS. He responded to topical treatment with clobetasol propionate alone.

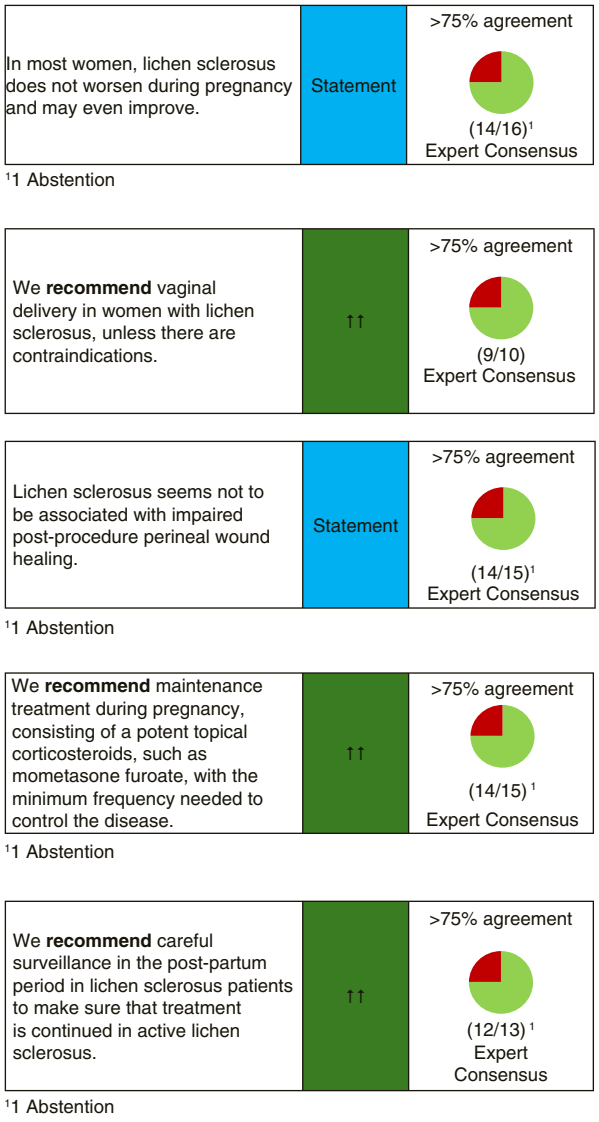
Urethroplasty

Urethroplasty of urethral strictures in LS is a challenging procedure and should only be performed by experienced urethral surgeons. In 1998, Venn presented a study comparing 12 one-stage pedicled penile skin-flap urethroplasties with 16 two-stage free graft urethroplasties using non-genital skin. All patients with pedicle penile skin urethroplasty had a recurrence of LS.[245] Moreover, an oral mucosa graft is regarded as the tissue of choice for urethroplasty of urethral strictures in LS.[211] Most commonly used are buccal mucosa grafts from one or both cheeks but mucosal grafts from the inner lips and even the tongue seem also suitable.[246] There are still authors advocating bladder mucosa or even colonic mucosa but this means an abdominal incision to harvest the graft.[247] In 2000, Depasquale et al. presented their 14-year experience and results of about 200 interventions on urethral strictures. They recommended the complete excision of diseased urethra and replacement by a mucosal graft in a two-stage procedure; no recurrences was observed during 1–9 years follow-up.[231] In recent years, most data support a more differentiated surgical strategy which consists of 'one-stage dorsal oral mucosa onlay graft' urethroplasty[218] extending the buccal mucosa grafts to the meatus thus creating a dorsal meatoplasty[248] in selected cases. If the stricture is limited to the penile urethra, the procedure can be performed by a circumcoronal incision, de-gloving the penile skin until proximal of the stricture. If the stricture extends beyond the penoscrotal junction (panurethral stricture), a midline perineal approach is used, followed by invagination of the penis as described by Kulkarni et al.[249] Dubey et al. recommend a one-stage dorsal buccal mucosa onlay urethroplasty if preliminary urethroscopy reveals a urethral calibre of more than 6 Fr and the urethral plate is not severely scarred.[248] Kulkarni and Barbagli et al. suggest using this technique as first choice if the following criteria apply:

- Age <70 years
- Primary repair
- Decreased urinary flow
- Histology showing slight or moderate disease, without cancerous or precancerous lesions
- There should only be focal involvement of the glans, penile skin and meatus
- The urethral plate should be viable or salvageable.

Success rates following this strategy are reported to be 80%–90% with a mean follow-up of 32–58 months.[235,248,250] One reason against the use of grafts (and in favour of flaps, which in LS is problematic) is the poor blood supply of the graft if placed as a ventral onlay. The dorsal onlay graft seems to solve this problem.[251] In older patients (>70 years), patients with previous multiple failed repairs, severe disease on histology, full involvement of the glans, penile skin and meatus and a scarred urethra a two-stage urethroplasty are recommended.[235,248,250] During the first stage, a perineal urethrostomy is made. The urethra is excised and mucosal graft applied. In the second stage, the neo-urethra is tubularized, connected with the proximal urethra and uerethrostomy is closed 4–6 months later. Kulkarni and Barbagli strongly suggest leaving the decision as to whether the second stage will be performed to the patient. Many elderly patients and patients with a long history of failed uerthroplasties are tired of multiple operations and may prefer to keep the perineal urethrostomy. But even then, a failure rate of 28% (recurrence, stenosis) is observed. Results of two-stage urethroplasty in accordance with the mentioned criteria have a higher rate of failure than the one-stage procedure, 27% in penile 2 stage urethroplasty.[235] The discussion concerning the best treatment of urethral stricture in LS is ongoing. Results of long-term follow-up (10 years) combined with analysis of quality of life of these patients are awaited.[235]

LICHEN SCLEROSUS IN PREGNANCY



We **cannot make a recommendation** with regard to the use of corticosteroid injection during pregnancy and breastfeeding in lichen sclerosus patients.	0	>50% agreement  (12/16) [1] Expert Consensus

[1]2 Abstention

Course of lichen sclerosus during pregnancy and lactation

Reports on LS course during pregnancy and its effect on delivery are scarce. Trokoudes and Lewis studied prospectively 36 pregnancies in 22 patients with LS. All pregnant women were treated with clobetasol propionate 0.05% ointment, 45% of women reported improvement of LS during pregnancy and needed less topical corticosteroids, and none experienced worsening of LS. There were 33 vaginal deliveries and three caesarean sections, due to failure to progress during delivery. Episiotomies were performed in nine women, of which three were related to assisted instrumental deliveries, 15 women experienced obstetric tears, and none developed LS in the obstetric scar or reported sexual dysfunction during follow-up of up to 4 years.[252] Similarly, in a survey of 45 women with LS, a total of 13 deliveries were reported, of which 12 were vaginal deliveries with episiotomy and one was a caesarean section.[253]

Also, Nguyen et al. report a favourable course of LS during pregnancy, of 33 pregnancies in 29 women, 27 had spontaneous vaginal births, 2 had instrumental deliveries for standard obstetric indications and 4 had caesarean sections, while only one of the latter was performed due to LS-related scaring in a non-compliant patient (good compliance was defined as always/mostly following treatment regimens). One woman developed LS in a perineal scar. All women were treated with topical corticosteroids, and their need of topical corticosteroids did not change during the course of their pregnancies. The authors stress that compliance to treatment during and after pregnancy is crucial to prevent relapses. Relapses only developed post-partum in patients who neglected topical corticosteroids treatment, likely due to physical and emotional distraction.[254]

A retrospective study by Kolitz et al. evaluated eight pregnant women with LS and reported that 63% were asymptomatic and 25% experienced exacerbation of symptoms during pregnancy. Two patients received no therapy and six were initially treated with topical corticosteroids; however, three of them discontinued treatment due to fear of harming the unborn child. There were three vaginal (two complicated by second-degree lacerations, not known if related to LS), four Caesarean deliveries (three of them because of obstetrical reasons, one because of unknown reason) and one without documented method of delivery.[255]

Günthert et al. evaluated the effect of oral contraceptives in 40 women with LS, four became pregnant and noted complete remission of LS during pregnancy.[26] Helm et al. showed a variable effect of pregnancy on LS, with half of the LS patients experiencing exacerbation and half improvement of LS symptoms.[256] Rarely LS is diagnosed during pregnancy, Haefner et al. documented two patients with newly diagnosed LS in pregnancy, and both women had spontaneous vaginal deliveries.[257] Nothing is known about their medical history; therefore, it cannot be judged if LS began before pregnancy. Finally, a population-based case–control study demonstrated no difference in number and type of vaginal deliveries, perineal suturing or perineal healing post-delivery between LS patients and the control group.[109]

What treatments are available for lichen sclerosus during pregnancy?

The gold standard for LS treatment are topical corticosteroids. However, the risk of foetal growth retardation following the regular use of ultrapotent topical steroids by the mother cannot be excluded; therefore, women are reluctant to use potent topical corticosteroids during pregnancy.[258,259] However, studies have shown that even ultrapotent topical corticosteroids used for prolonged periods to treat LS are safe, because the treated area is small.[43]

Topical calcineurin inhibitors are not licensed for pregnant or breastfeeding women.

Systemic retinoids are severely teratogenic, and their use in women of childbearing age is strictly regulated; for safety reasons, also topical retinoids must not be used in pregnancy.

Perineal injury and scarring may trigger LS. Long-term effects of perineal injury on LS have not been studied well. The risk of potential injury or episiotomy during vaginal delivery may be reduced by antenatal perineal massage, and it should be recommended to all pregnant women independent of the presence of LS.[260]

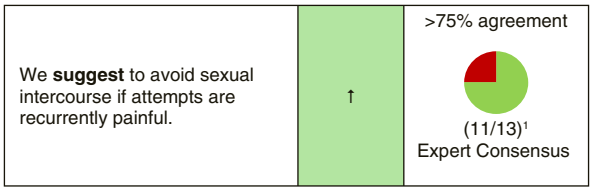
Recommendation for treatment during pregnancy

There is no objection to occasional use of topical corticosteroids in genital LS (e.g., once or twice a week); however, potent topical corticosteroids (e.g., mometasone furoate) are preferred to very potent topical corticosteroids (clobetasol propionate) during pregnancy.[261]

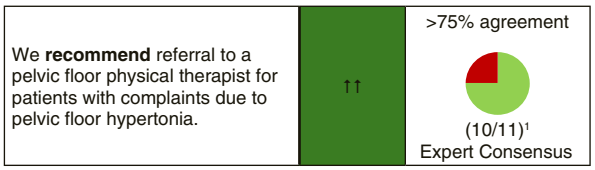
All other treatments are not recommended during pregnancy and lactation.

PAIN IN LICHEN SCLEROSUS

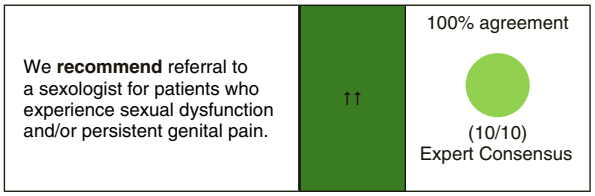
We **recommend** considering potential trigger factors for genital pain such as urine exposure or mechanical friction in patients with lichen sclerosus.	↑↑	100% agreement  (14/14) Expert Consensus



[1]2 Abstention



[1]1 Abstention



Introduction

Patients with LS may experience local genital pain due to LS which will have a negative impact on sexuality.[262] Urinary exposure can trigger or worsen pain in patients with LS, just like sexual touching and sexual intercourse. Males with LS having penetrative sex can notice penile pain (dyspareunia). Women with LS having penetrative sex can notice vulval pain (dyspareunia). If painful sex encounters, especially when recurrent and prolonged, it can lead to insufficient arousal and/or secondary pelvic floor hypertonia. In males, insufficient arousal can cause erectile and orgasmic dysfunction. In females, insufficient arousal can lead to insufficient lubrication and orgasmic dysfunction. Chronic pain can lead to a chronic pain syndrome with peripheral (neuroproliferation) and central (neuromodulation) sensitization, described in women with vulvodynia.[263,264]

Secondly, women and men with genital LS report numerous bladder, bowel and pain comorbidities.[265] Characteristically bacterial infection can be excluded, and treatment is challenging. It is not known if measures that are taken in interstitial cystitis including laser treatment may be helpful in this LS-related bladder pain.[266] Further study of these comorbidities with standardized screening instruments in the LS population is needed. Additionally, practitioners should be cognizant of these associated disorders and consider screening in patients with LS.[267]

Genital pain (either due to active LS or by urinary or physical triggering), sexual dysfunction and pelvic floor hypertonia can maintain or even reinforce each other. Genital pain may be not only associated with somatic aspects but also with psycho/social and sexual dysfunction. Management of genital pain requires not only attention for somatic/pain-medication treatment but also attention for psychosocial and sexual health and attention for pelvic floor muscle rehabilitation.

Genital pain in women

The ISSVD (International Society for the Study of Vulvovaginal Disease) classifies chronic vulval pain[268] in:

- Vulval pain due to somatic disease. This may be vulval pain directly due to active LS and is expected to improve or dissolve on successful treatment of the LS.
- Vulvodynia: non-somatic vulval pain.

The ISSVD emphasizes the occurrence of somatic vulval pain in combination with vulvodynia.

In clinical practice, two types of vulvodynia are distinguished:

Localized provoked vulvodynia is more common in young women and is characterized by longstanding or recurrent pain at (attempt to) coitus/penetration. When examining these patients, localized areas which are (extremely) painful to even minimal palpation are found in the vestibulum. The pelvic floor is hypertonic and can be carefully examined by inspection (ask if the woman is able to contract and relax her pelvic floor muscles) or by outer palpation of the perineal body. Vaginal digital examination—if possible—can confirm hypertonia. Vaginal pelvic floor hypertonia can be a reflex of the vaginal musculus pubococcygeus but can also be more or less permanent and generalized through the whole pelvic floor. This may be associated with problematic defaecation (constipation) and voiding.

Counselling should consist of education about LS and education about requirements for successful intercourse, such as:

- Physically healthy vulval and vaginal epithelium which can withstand penile-vaginal friction;
- Sexual desire and arousal for lubrication of vulva and vagina; referral to a sexologist may be indicated.
- Relaxation of vaginal pelvic floor muscles for compliance enabling the penis to enter; referral to a specialized pelvic floor physical therapist may be indicated.

Generalized spontaneous vulvodynia is more common in peri- and postmenopausal women and is characterized by chronic (>3 months) 'burning' vulval pain, independent of coitus or palpation. The pain is neuropathic in presentation, often radiates to the vagina, anal area, abdomen, bladder or thighs, and worsens when sitting on a hard surface. It may be associated with other pain syndromes.

Treatment consists of counselling in combination with medication used for other types of neuropathic pain such as amitryptiline, nortriptyline, gabapentine and pregabaline. Even low doses may be effective.

Genital pain in men

In men, genital pain (penodynia) may also be caused by (a combination of) pain due to active LS, irritation of the penile glans by sexual activities, pelvic floor hypertonia and genital dysaesthesia.

To reduce LS-related pain, LS treatment should be optimized to achieve a healed epithelium that can withstand friction.

If neuropathic pain is part of the problem, counselling in combination with medication used for other types of neuropathic pain such as amitriptyline, nortriptyline, gabapentin and pregabalin is recommended. Even low doses may be effective.

If pelvic floor hypertonia is part of the problem, the patient should be referred to a specialized pelvic floor physiotherapist.

If sexual desire, arousal and erectile function are part of the problem, referral to a sexologist may be indicated.

FOLLOW-UP

We **recommend** regular follow-up examinations for lichen sclerosus patients; initially e.g. every 1 to 6 months until the disease has stabilized, and once stable, e.g. once a year.	↑↑	100% agreement (15/15) Expert Consensus
We **suggest** that patients with mild lichen sclerosus could be monitored by general practitioners and through self-monitoring.	↑	>75% agreement (15/16) Expert Consensus
We **recommend** that all children with lichen sclerosus are followed by a specialist with expertise in treating lichen sclerosus.	↑↑	100% agreement (15/15) Expert Consensus
We **recommend** that all adult lichen sclerosus patients who do not respond to treatment with potent topical steroids or who have precancerous lesions of the vulva or penis are followed by specialists, e.g. dermatologists, gynaecologists or urologists.	↑↑	100% agreement (15/15) Expert Consensus
We **recommend** that lichen sclerosus patients with voiding problems are referred to an appropriate specialist, such as a urologist or urogynaecologist.	↑↑	100% agreement (15/15) Expert Consensus
For the follow-up of lichen sclerosus patients, we **recommend** the following: • monitor treatment effectiveness (including symptom relief/ control, normalisation of skin colour and texture), • ask about problems in voiding, defaecation and sexual function, • monitor for the development of precancerous or cancerous lesions, • ensure adherence to treatment.	↑↑	100% agreement (15/15) Expert Consensus
We **recommend** that patient education includes • recognition of lichen sclerosus changes that point towards disease progression or cancer development (ulceration, non-healing lesions, papules, wart-like lesions), • information about the importance of adherence to treatment to help prevent disease progression, • avoidance of trigger factors, • awareness of symptoms of autoimmune diseases (e.g. thyroid disease).	↑↑	>75% (13/14) Expert Consensus

LS has a potential for spontaneous or treatment related remission but can, if untreated, progress to irreversible structural changes in the affected anogenital site, including resorption of labia minora, agglutination of the clitoral hood, phimosis, stenosis of introitus vaginae and meatus urethrae or stricture, and patients with LS have a risk of developing squamous cell carcinoma. Gold standard of treatment for LS are potent topical steroids. Follow-up is needed for the evaluation of the treatment effect, compliance, disease progression, side effects of the treatment and signs of (pre-) cancerous lesions.

Clinical examination and frequency

Structural changes of the affected anogenital skin are one main concern in LS patients as these changes may lead to female and male dyspareunia and micturition disorders.[11,269,270] The clinical examination at the first visit should ideally include a clinical photograph as a starting point for comparison in follow-up visits.

Treatment early in the disease course can induce symptom relief/control, normalize the skin colour and texture especially in children,[224,271–273] whereas in longstanding disease where scarring occurred the treatment goal is symptom control, reducing progression of scar formation and screening for squamous cell precancer and cancer.[43] A close follow-up is needed in the early stage preferably within 3 months after the initial consultation to ensure treatment efficacy, potential side effects (atrophy due to

topical steroids, irritant or allergic reactions) and compliance.[43] A large prospective study of 507 women with vulval LS showed that almost 30% of the women were only partially compliant to treatment. Significantly more of these partially compliant woman showed vulval adhesions or scarring compared with treatment compliant women.[43] Likewise two studies in prepubertal girls assessing the benefit of adherence to long-term treatment showed that a high percentage of girls achieved complete disease suppression in contrast to girls who did not adhere to long-term treatment.[43,271] These studies underline the importance of treatment and compliance to treatment. The goal of treatment has to be explained at follow-up visits, and the supply of treatment must be guaranteed. Follow-up also includes inquiries about changes in miction, defaecation and sexual function. Change in defaecation can lead to constipation. If changes in miction/voiding are reported the patient should be referred to an urologist or urogynaecologist. The urological investigation should include an uroflowmetry. If this shows an obstructive pattern or the patient has a clear meatal stenosis, a retrograde urethrogram should be performed to exclude a distal urethral stricture (which may be caused by LS) or another pathology responsible for the urological symptoms. Early treatment of inhibited micturition will prevent further complications.[274]

After the initial follow-up, LS patients should be seen regularly, for example, every 3–6 months for 2 years and if the disease is stable follow-up visits may be scheduled once a year.[43] Mild LS in adults might be followed up by the general practitioner or local gynaecologist, next to self-monitoring. All children with LS and adults unresponsive to treatment with a potent topical steroid or if vulval or penile precancer or cancer is an issue should be followed up by a specialist, specialized in anogenital skin diseases.

For decades, a common perception was that LS would remit at puberty, but this has since been challenged and remission of LS in childhood might be determined more by early successful treatment than by hormonal factors.[272,273] We do not know in how many children with LS the disease will continue in adult life. Current data suggest that even if remission has occurred in childhood or puberty, follow-up in adult life should be ensured, at least in females.[275]

LS may be associated with a number of diseases, namely autoimmune diseases in women (see chapter 1 introduction, section on associated diseases).

UPCOMING TREATMENTS

In the past decade, the advent of biologics (e.g., TNFalpha inhibitors, anti-IL-2, -4, -12, -13, -17, -22, -23, -36 and IgE directed therapies) and small molecules (e.g., apremilast and janus kinase (JAK) inhibitors) changed the treatment of inflammatory skin diseases such as psoriasis, atopic dermatitis or chronic urticaria fundamentally. Some of these new drugs have also been used off label in other inflammatory skin conditions with promising effect including mucosal lichen planus (LP).[271,276–279]

Costs and adverse effects have to be considered, but higher costs may be justified in conditions which cause irreversible scarring and impact significantly on quality of life. It still needs to be established if such treatments have an effect on cancer development in mucosal LP.

However, these novel drugs have not been studied in LS, indicating both an unmet need and an unexplored large therapeutic potential with marketed drugs.

Therefore, the use of these drugs in LS can currently not be recommended. However, an off label use of topical or systemic JAK inhibitors, apremilast or tildrakizumab, may be justified in patients with vulval LS provided they suffer from an overlap with mucosal lichen planus.

According to clinicaltrials.gov (April 2022), no clinical trials on systemic treatments in LS are planned, ongoing or completed. The majority of trials listed in this register deal with laser-based techniques or topical treatments, mainly corticosteroids or topical calcineurin inhibitors. Several ongoing or completed trials are on autologous platelet-rich plasma, photodynamic therapy and UVA1 in vulval LS. These trials are important, as they will help to increase the still low evidence of these treatment modalities in LS. Remarkably, to date there is no study registered on clinicaltrials.gov addressing male LS, paediatric LS or extragenital LS, highlighting the need for coordinated multi centre initiatives to conduct studies including all LS populations.

Lichen sclerosus on clinicaltrials.gov, searched in April 2022

$N = 35$ (of which four were also for other vulval diseases)

- Biomarkers in vulval LS
- Mona Lisa Touch Laser versus Clobetasol in VLS (completed)
- Injection of autologous fatty tissue associated with autologous platelet-rich plasma (completed)
- Fractional CO_2 plus PDT in VLS
- VLS influence on quality of life (completed)
- Nd:YAG laser versus topical betamethasone in VLS
- Microbiome in postmenopausal VLS
- CO_2 Laser plus topical steroids versus topical steroids only in VLS $n = 3$ (completed)
- Platelet-rich plasma for VLS $n = 2$ (completed)
- Clobetasol propionate versus PDT and versus low intensity laser in VLS (completed)
- 2940 nm fractional laser for VLS
- Fractional CO_2 in VLS $n = 3$ (two completed)
- Rivelin plain patches in VLS (completed)
- Vulval scarring grading scale for LS (completed)
- Progesterone versus clobetasol propionate in VLS (completed)

- Clobetasol propionate versus UVA1 in VLS (completed)
- Clobetasol versus pimecrolimus for VLS (completed)
- Clobetasol propionate versus tacrolimus (completed)
- Dual laser for VLS (completed)
- AI temperature-controlled radiofrequency technology and electrical stimulation in vulval leukoplakia/VLS
- Low level laser to improve quality of life in VLS (completed)
- Early detection of vulval cancer through self-examination (EDuCATE) Intervention Study
- Ruxolitinib Cream (JAK inhibitor) NCT05593445 (recruiting)

  - Most studies are on laser-based treatments and topical treatments (corticosteroids, topical calcineurin inhibitors).
  - NO study on male LS
  - NO study on paediatric LS
  - NO study on systemic treatment

A further issue is the delayed diagnosis of LS. This often leads to therapeutic delay and development of scarring and genital cancer. A study is underway that aims to develop the digital recognition of LS supported by artificial intelligence https://www.wohlva.ch/. A cell phone application will offer digital recognition of LS; it will then give stratified recommendations. This may reinforce patients who are ashamed of their genital problem to seek professional medical help rather sooner than later.

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ACKNOWLEDGEMENTS

The authors like to thank the physicians and specialists who contributed to the development of this guideline. We especially thank the British Association of Dermatologists for providing the data from their systematic review. They kindly agreed to utilize and update this data, which formed the evidence base for our guideline.

FUNDING INFORMATION

This EuroGuiDerm guideline was funded through the EuroGuiDerm Centre for Guideline Development. The European Dermatology Forum is responsible for fundraising and holds all raised funds in one account. The EuroGuiDerm Team is not involved in fundraising or in the decision making on which guideline (GL) or consensus statement (CS) development is funded. The decisions on which GL/CS is funded are made by the EuroGuiDerm Board of Directors independently. The EDF or any other body supporting the EuroGuiDerm is never involved in the guideline development and had no say on the content or focus of the guideline.

CONFLICT OF INTEREST STATEMENT

This is a brief summary of the update of the EuroGuiDerm Guideline on Lichen sclerosus. For the complete guideline, methods report (including COI disclosures) and evidence report see https://www.guidelines.edf.one/edf-guidelines-and-consensus-statements.

DATA AVAILABILITY STATEMENT

The data that support the findings of the systematic review are available in the evidence report of the guideline (https://www.guidelines.edf.one/edf-guidelines-and-consensus-statements).

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How to cite this article: Kirtschig G, Kinberger M, Kreuter A, Simpson R, Günthert A, van Hees C, et al. EuroGuiderm guideline on lichen sclerosus—Treatment of lichen sclerosus. J Eur Acad Dermatol Venereol. 2024;00:1–36. https://doi.org/10.1111/jdv.20083