European Dermatology Forum

Guideline on Lichen sclerosus

Developed by the Guideline Subcommittee of the
European Dermatology Forum

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Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus

Running head: S3 Guideline on Lichen sclerosus
Synonyms: lichen sclerosus et atrophicus, lichen albus, hypoplastic dystrophy, kraurosis vulvae, white spot disease and balanitis xerotica obliterans in males

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Disclaimer: These recommendations reflect the best data available at the time the report was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from these recommendations in special circumstances. Just as adherence to guidelines may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligent.

Summary of Recommendations
All patients with symptoms or signs suspicious of lichen sclerosus should be seen at least once initially by a physician with a special interest in the disease to avoid delay in diagnosis as early treatment may cure the disease in some and reduce or prevent scarring.

Biopsies should be performed

- if the clinical diagnosis is in doubt,
- if recommended first line treatment fails after appropriate treatment duration,
- if malignancies are suspected,
- it is not necessary to biopsy everyone; however when performed, the reason for the biopsy should be documented.

Currently there is no single strategy (medical or surgical) that can be recommended for the treatment of LS. Patients and their parents or "carers" should be informed of the different options and their advantages and disadvantages explained enabling them to make a decision. The treatments that have been used and their efficacies are documented in the summary table 1.

For genital LS in females potent to very potent topical steroids remain the treatment of choice. Randomized controlled trials compared the effect of very potent and potent topical corticosteroids with other treatment modalities; in all studies topical steroids were most effective in the treatment of female genital LS. Cure is not usually the aim of treatment but improvement of symptoms (75%-95%) after three months or at its best reversals of signs (20%) (1+ / A). Usually early LS responds better to treatment compared to late disease; scarring is irreversible.

For genital LS in males early diagnosis and prompt cure of LS is the aim. The aim of treatment is complete abolition of signs and symptoms leading to normal sexual and urinary function. This may lead to a reduction in the risk of cancer. In mainly retrospective studies or studies with only a few years follow-up circumcision is claimed to be curative in most cases of early and intermediate LS in males (nearly 100% in boys), restricted to prepuce and glans (3+ / D). Regression of symptoms is usually seen 4-8 weeks after circumcision; in most 4-6 months later LS has healed, it may, however, take up to 2 years. Good long-term follow-up studies (more than 10 years) are lacking therefore the rate of recurrences years after circumcision remains undetermined. However, an initial curative attempt with topical corticosteroid treatment should be offered, e.g., with potent to very potent topical steroids for three months dayly; follow-up after one month in mild cases seems reasonable to adjust treatment and avoid adverse effects (skin atrophy) if necessary. In early and mild cases cure can be achieved and the prepuce preserved (41-76% improvement, cure claimed in about 50%). However,follow-up is recommended as recurrences 5 years after medical treatment are observed. Continuing signs and symptoms of LS after medical treatment are not acceptable as surgical treatment can result in a symptom free patient. In more complex cases with urethral involvement reconstructive surgery may be necessary and provides good results if performed by experienced urethral surgeons.

Initial treatment with topical steroids:
There is no standardized treatment regimen; often clobetasol propionate 0.05% ointment (or cream) once or twice daily for 3 months with a possible reduction of application frequency after one month in milder cases is applied. Usually a finger tip per application and a maximum amount of 10 g per month (possibly a little more for initial treatment) is recommended to avoid skin thinning. Maintenance treatment with either topical steroids or calcineurin inhibitors is recommended as it seems to prevent severe relapses in some; both treatments do not seem to be associated with severe side effects even when used long-term, unless used in excessive amounts. Moisturizers improve symptoms in about 10%; silk underware was associated with fewer symptoms compared to cotton underware, this may point towards a worsening of symptoms due to mechanical irritation. Both moisturizers and avoidance of mechanical triggers should be recommended.
In treatment resistant LS several options may be tried and are dependent on sex, age and other individual circumstances: topical and oral retinoids, steroid injections, ciclosporin, methotrexate, and

hydroxyurea. Some of those treatments are associated with severe side affects. Stem cell transplants combined with platelet rich plasma is decribed but needs further evaluation. Surgery in females is reserved for complications of LS such as functional impairment or development of in situ or invasive cancer.

Maintenance treatment:
If symptoms recur steroid ointment should be used as directed. For maintainence and to remain almost symptom free some people only need to use the ointment once or twice a month, others may require to use it twice or three times a week. Proactive maintenance therapy with twice-weekly application of mometasone furoate 0.1% ointment was effective and safe in maintaining remission (1+ / A).
To avoid skin thinning no more than one30 g tube of strong steroids (e.g. 30g clobetasol propionate 0.05% ointment or mometasone fuorate 0.1% ointment) should be used in 3 months. There is no such recommendation available for calcineurin inhibitors.

For **treatment-resistant LS**, mainly applicable for females, various treatments are available. Topical and oral retinoids, methotrexate and possibly local steroid injections for single lesions seem the safest and perhaps most effective options.

Follow-up:
The first follow-up should be at three months but needs to be adjusted in an individual situation. For stable uncomplicated disease, follow-up after 6 months may be appropriate. Patients with LS and VIN/CIN/PIN or cancer should remain under specialist follow-up other patients may be seen by their GPs; follow-up modalities may vary between countries.

Further recommendations:
Topical corticosteroid treatment should be simplified to the regime documented in the guidelines unless contraindicated. The topical steroid should be weaned by frequency of application and not necessarily potency to avoid the use of multiple preparations which can cause confusion. However, some may prefer weaker steroids instead, in particular in children.

Patients should be instructed to use emollients and avoid any irritation of the genital skin (cleansing products, frequent exposure to water, incontinence , cloths, some may find that sports such as cycling / riding a horse etc. may exacerbate their symptoms).

Oral contraceptive pills with anti-androgenic properties may be associated with an increased risk of LS.

Photographs should be utilized as a clinical tool to assess disease progression whenever possible.

All patients must be made aware of the increased risk of squamous cell carcinoma. Ideally all patients should receive a patient information leaflet and this must be documented.

All patients with a confirmed diagnosis of LS should be made aware of the possibility that family members may have LS too and members with symptoms pointing towards LS should be inspected.

LS in women is known to be associated with autoimmune diseases; in addition to clinical evaluation some recommend screening for associated autoimmune diseases with an autoantibody screen and thyroid status.

What's already known about this topic?

- Lichen sclerosus is a common but underdiagnosed condition of the anogenital area
- It is often painful and itchy (females) and may cause sexual and urinary dysfunction
- It is associated with anogenital squamous cell carcinoma.
- The current treatment of choice is potent topical steroids in women; however, it is not known if they influence its prognosis.
- In men the first line treatment recommendations are disputed some physicians recommend topical steroids others early circumcision.
- It is proposed that early treatment may lead to cure of LS.
- Since the establishment of topical steroids in the treatment of LS other treatment modalities have only been sparsely investigated.
- Treatment modalities may vary between specialties.

What does this study add?

- This guideline was developed by an international, multidisciplinary panel of experts in LS
- It aims to highlight potential triggers for LS
- Advice on initial management
- Advice on current treatment options with best long-term outcome for females and males
- Future research strategies.

What is the goal of the treatment in Lichen sclerosus?

Females:

- Currently, treatment mainly aims for suppression of symptoms like pruritus and signs such as pallor, erythema and fissures in vulval LS.
- Ideally treatment that prevents scar formation, sclerosis and atrophy as well as development of cancer is desired.
- Spontaneous remission of LS may occur, however, treatment induced cure / permanent remission is rarely described

Males:

- In boys and early disease in men cure may be achieved.
- Cure, i.e. no symptoms and signs of LS after treatment without recurrence for many years / indefinitely in the majority is described but good long-term studies to prove this are lacking.

Main questions that panel members sought to be answered:

- Triggers for lichen sclerosus? What needs to be avoided?
  - Trauma: how important is it?
    LS is known to occur after surgery etc. Does this mean trauma in predisposed individuals plays an important role?
    - ✓ **Boys:** An initial (small) trauma like preputiolysis or balanopostitis, e.g., as maneuvers of "mechanical reduction of the foreskin" performed at least 5-10 times per month are reported in boys with LS.(Villa 2012)
    - ✓ Hypospadias repair is linked with (and complicated by) LS.
  - However, circumcision in early childhood / men seems associated with less LS in later life?
    - ✓ **Boys / Men:** Bunker and co-workers propose the theory that irritation by urine is a major factor in precipitating and localizing genital LSthe pivital factor is irritation by urine.(Edmonds 2012)

- Is there a **cure** (no disease progression in the absence of treatment) for LS?
  - **Boys / Men**: Does early and "complete" circumcision in boys / men prevent extensive disease (e.g. extension to urethral involvement?)
    - ✓ There is some evidence that circumcision leads to high cure rates in mild to intermediate LS in men and boys ("cure" in nearly 100% of boys is described).(Depasquale 2000; Kiss 2005; Kulkarni 2009, Becker 2011)
    - ✓ Do we need a RCT in boys/men to determine if clobetasol or early complete circumcision will lead to a higher cure rate? A RCT comparing a medical versus surgical intervention may be difficult to perform.
  - **Females:**
    - ✓ There is no good hint from the current literature that LS can be cured in many female patients by any treatment. However, cure can possibly be achieved in early disease after potent topical steroid treatment or there may be spontaneous remission (probably mainly in girls).

- How do we achieve **good long term results**?
  - **Boys / Men**: The aim is cure in early disease
    Can we recommend early circumcision if e.g., an initial trial of potent to very potent topical steroids for three months has failed?
    - ✓ Circumcision of mild to intermediate LS in males offers "cure" in nearly 100% for boys. However, controlled long-term studies are lacking. Retrospective studies covering 10 years follow-up show remission after complete circumcision.(Becker 2011)
  - **Females:** a good result is defined as no scarring/stenosis, no pain (erosions, fissures, dyspareunia), no itch
    Best to achieve this:
    - ✓ Early treatment with potent to very potent topical steroids for three months (Chi 2011, Lorenz 1998, Bracco 1993, Dalziel 1993, Powell unpublished data)
    - ✓ Maintenance treatment with topical steroids or calcineurin inhibitors (Virgili 2012)to suppress symptoms like pruritus and invisible/not symptomatic inflammation at any time

- What is the **risk of long-term treatment**?
  - ✓ There is an intrinsic risk in LS to develop anogenital malignancies.
  - ✓ There is no evidence from the literature that there is an increased risk of anogenital malignancies after long-term treatment (either with steroids nor for calcineurin inhibitors, however very long term follow up studies are not available).

- Is there a good treatment for **existing scars** /sclerosis like meatal stenosis / burying of the clitoris?
    - ✓ In functional impairment surgery performed by experts after careful consideration may be adviced
    - ✓ Fat stem cell transplants plus platelet enriched plasma is in development, published results are awaited

- What is the risk of **cancer development** in LS when/if long-term treatment with very potent topical steroids / tacrolimus / picroliminus are applied compared to occasional, non-continuous treatment e.g. only in symptomatic LS?
    - Is there an intrinsic risk for cancer development in LS?
        - ✓ Yes, as e.g. reported by Wallace when potent topical steroids did not exist
    - Is it chronic inflammation that causes cancer?
        - ✓ Possibly, but this is not known.
    - Is, therefore, treatment of LS in males with anti-inflammatories recommended and preferred to circumcision?
        - ✓ An initial curative attempt with anti-inflammatory durgs can be tried, otherwise surgery is recommended as it seems to be curative in many and therefore reduces the risk of / prevents cancer and progression into urethral disease with potentialyl irreversible damage.

- Future treatment developments?
    - LS is a Th-1 mediated disease. This means that treatments that interfere with e.g. interferon gamma or TNF alpha may be potential treatment options for LS and LP; comparable to treatments for psoriasis. Systemic treatments have rarely been used in vulval LS, however, in severe cases systemic treatment with systemic steroids, fumarates, MTX, ciclosporine or anti-TNF acting bilogicals may be justified, further studies are needed to explore efficacy.
    - An interesting option may be the PDE-antagonist Apremilast (PDE = phosphodiesterase which breaks down cAMP). Cell activity inhibition with a PDE-antagonist will increase cAMP in cells and will inhibit TNF-alpha production, comparable to Pentoxyfylline (Trental). However, Pentoxyfylline in contrast to Apremilast is not very specific for T-cells and is accompanied by many adverse effects.
    - It was suggested that agents with the potential of increasing epidermal CD44, like retinoids, should be tried in LS.

- What treatments should be compared in a future RCT?
    - Circumcision versus potent topical steroids in boys with penile LS:
        - ✓ The evaluation of prospective case series with high numbers and long follow-up may replace an RCT which may prove difficult to perform?
        - ✓ However, ideally a randomized study may compare potent topical steroids for three months (possibly followed by circumcision after 6 months in patients who failed to respond to medical treatment) with immediate circumcision to judge the short-term effect of the two treatments (a biopsy to confirm LS prior to treatment may be a too big burden for the patient, good clinical criteria need to be adhered to).
    - Hydroxycarbamide or oral retinoids in treatment resistant LS.
    - Topical steroids alone vs topical steroids plus topical oestrogen in postmenopausal vulval LS.
    - Maintenance treatment with either topical tacrolimus or steroids once or twice a week vs emollients only after initial Rx with potent steroids for year.
    - Topical retinaldehyde 0.05% vs clobetasol propionate vs placebo: What change in histology, hyperkeratosis, scarring, dyspareunia can be observed after 3, 6, 12 months treatment?

Search strategy:
Searched libraries: MEDLINE, MEDLINE process, Embase, Cochrane library
Search date: 28th of October 2013, no date limitation.
MEDLINE search for randomized controlled trials
1. exp Lichen Sclerosus et Atrophicus/
2. (lichen adj3 (scleros* or atrophi* or albu* or scleureu* or sclero-atrophi* or vulva* or genita*)).ab,ti.
3. "white spot* diseas*".ab,ti.
4. exp Vulvar Lichen Sclerosus/
5. "kraurosi* vulva*".ab,ti.
6. (vulva* and (atroph* or dystroph*)).ab,ti.
7. exp Balanitis Xerotica Obliterans/
8. balaniti* xerotic* oblitera*.ab,ti.
9. "kraurosi* peni*".ab,ti.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. Randomized Controlled Trials as Topic/
12. randomized controlled trial/
13. Random Allocation/
14. Double-Blind Method/
15. Single Blind Method/
16. clinical trial/
17. clinical trial, phase I.pt.
18. clinical trial, phase II.pt.
19. clinical trial, phase III.pt.
20. clinical trial, phase IV.pt.
21. controlled clinical trial.pt.
22. randomized controlled trial.pt.
23. multicenter study.pt.
24. clinical trial.pt.
25. exp Clinical Trials as topic/
26. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. (clinical adj trial$).tw.
28. ((singl$ or doubl$ or treb$ or tribl$) adj (blind$3 or mask$3)).tw.
29. Placebos/
30. placebo$.tw.
31. randomly allocated.tw.
32. (allocated adj2 random$).tw.
33. 27 or 28 or 29 or 30 or 31 or 32
34. 26 or 33
35. case report.tw.
36. letter/
37. historical article/
38. 35 or 36 or 37
39. 34 not 38
40. 10 and 39

MEDLINE search for case reports
1. exp Lichen Sclerosus et Atrophicus/
2. (lichen adj3 (scleros* or atrophi* or albu* or scleureu* or sclero-atrophi* or vulva* or genita*)).ab,ti.
3. "white spot* diseas*".ab,ti.
4. exp Vulvar Lichen Sclerosus/
5. "kraurosi* vulva*".ab,ti.
6. (vulva* and (atroph* or dystroph*)).ab,ti.
7. exp Balanitis Xerotica Obliterans/

8. balaniti* xerotic* oblitera*.ab,ti.
9. "kraurosi* peni*".ab,ti.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Cohort Studies/
12. "cohort*".ab,ti.
13. exp Epidemiologic Methods/
14. exp Case-Control Studies/
15. "case* control*".ab,ti.
16. "case* serie*".ab,ti.
17. exp Case Reports/
18. "case* report*".ab,ti.
19. "case* stud*".ab,ti.
20. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 10 and 20

Evaluation of articles using GRADE:
http://www.gradeworkinggroup.org/

Level of evidence and grade of recommendation

Level of evidence	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal[a]
3	Non-analytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

[a]Studies with a level of evidence '–' should not be used as a basis for making a recommendation.
RCT, randomized controlled trial.

Grade of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1 + +, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1 +, directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2 + +, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1 + + or 1+
C	A body of evidence including studies rated as 2 + , directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2 + +
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2 + , or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial; NICE, National Institute for Health and Clinical Excellence.

Introduction

Lichen sclerosus (LS) is an inflammatory skin disease that usually involves the anogenital area where it causes itching and soreness, sexual dysfunction, urinary dysfunction in men and is associated with genital cancer. The course of LS can be chronic. Treatment remains unsatisfactory, in particular in women as disabling scar formation is common despite treatment.(Green 2013; Balasubramaniam 2007, Cooper 2004, Powell 1999)

Lichen sclerosus is possibly underdiagnosed; it is a disease commonly seen in "vulval" and "penile" clinics and accounts together with spongiotic dermatitis and other lichenoid interface dermatoses for the majority of specimens in pathology departments investigating foreskins.(West 2013)

This guideline aims to highlight potential triggers for LS, to offer advice on current treatment options and to suggest future research strategies.

Clinical features of lichen sclerosus

LS is a chronic disease with waxing and waning symptoms. Itch is the main complaint in genital LS in women; sexual and urinary dysfunction in men.

The primary lesions are flat ivory-coloured spots, which may merge together into crinkly thin (skin atrophy) or hyperkeratotic patches. On the vulva or penis we often see an erythema next to depigmented spots (either hyperkeratotic or sclerotic) and fissures. Purpura or ecchymoses are typical and harmless but for some patients distressing features of LS. The Köbner phenomenon that describes the development of lesions in previously normal skin after scratching or other trauma is well recognized.(Wallace 1971) Scarring is common and is observed in about 80% of women and 30% of girls with LS.(Cooper 2004) It may lead to loss and agglutination of the labia minora possibly midline fusion with loss of the clitoral hood and narrowing of the vaginal introitus. Perianal involvement is typical in females, rarely seen in males, showing erythema, skin atrophy or sclerosis with erosions and fissures, or rarely scarring possibly leading to anal stenosis. Women commonly report itching, burning pain, painful or less pleasurable sexual intercourse, and anal or genital bleeding due to fissuring of the damaged tissue. Painful defecation may be a problem (fissures), especially in children, causing constipation.(Marren 2005) Soft stools after a fiber rich diet may help.

Lichen sclerosus in men and boys usually occurs on the glans penis and/or foreskin, with a predilection in the perifrenular aerea, and may cause phimosis in a previously retractable foreskin or adhesions of the foreskin to the glans causing dysuria or painful erection. Perineal involvement in men is rarely observed. Meatal stenosis may lead to problems passing urine and urinary obstruction; urethral disease can be a severe complication. LS in men is thought to more frequently affect uncircumcised or late circumcised men and occurs only rarely in those who were circumcised at birth.(Ledwig 1989; Edmonds 2012) Early and complete circumcision is thought to be the treatment of choice in affected boys; if this is preferable to treatment with very potent topical steroids needs to be evaluated.(Meuli 1994; Kiss 2001; Vincent)

Lichen sclerosus at the extra-genital skin alone is rare and has been reported in about 6% of all affected women (Wallace 1971). Involvement of the scalp, including bullous variants and scarring alopecia, is rare but reported.(Marren 1992; Basak 2002; Madan 2009) It is generally taught that LS does not affect the oral mucosa, nails or vagina, however, the occurrence at these sites is reported.(Meffert 1995; Schulten 1993; Tremaine 1989; Ramrakha-Jones 2001; Zendell 2013; Bhargava 2013)

The diagnosis of anogenital LS in most cases is made clinically, but a confirmatory biopsy is helpful if there is clinical doubt about the diagnosis and to detect any atypical or malignant changes.

Differential diagnosis

"Mucosal" or erosive lichen planus is the main differential diagnosis. GvHd, inverse psoriasis, eczema, vitiligo (particularly difficult in children), morphea, plasma cell vulvitis/balanitis, VIN / PIN and SCCs may show clinical features resembling LS. If the diagnosis is in doubt, a vulval biopsy has to be performed.(Raj 2013)

Infections and a contact dermatitis may be superimposed, and these should be treated.

Histological features

A biopsy is not necessary in all patients in particular if the clinical picture is diagnostic. In children a vulval biopsy is not usually performed, because it may be very traumatic for the child. It should be reserved for cases with an uncertain diagnosis and thosewho fail to respond to treatments.(Neill 2010)
Typical histological features of LS are orthohyperkeratosis, epidermal atrophy, basal cell degeneration, dermal hyalinisation, and a band like lymphocytic infiltrate.(Niamh 2009) However, in early LS some features like the hyalinisation of the upper dermis may be lacking and a firm diagnosis cannot be made. Also, mucosal / erosive vulval liken planus may show similar clinical and histological features making a distinction between the two diseases impossible in some cases.
Comparing LS and LP there are features more commonly seen in LS than LP and vice versa see table.

Table 2 summarizing histological differences between lichen sclerosus and lichen planus (Fung 1998)

	LS % with stated feature	LP % with stated feature
psoriasiform lichenoid pattern	100	0
basilar epidermotropism	78	0
loss of papillary dermal elastic fibers	100	33
basement membrane thickening	44	0
epidermal atrophy	33	0
many cytoid bodies	0	100
wedge-shaped hypergranulosis	11	100
basal squamatization	25	100
pointed rete ridges	11	83

Epidemiology
Incidence / prevalence
The exact prevalence of LS is unknown. The suspected prevalence varies between 0.1% and 3% for children and old women respectively.(Goldstein 2005; Tasker 2003; Leibovitz 2000; Wallace 1971) Extrapolation from the Oxford clinic data suggests that approximately 150 to 200 women per million population present each year.(Clayton 2006) The incidence in males was estimated to be 0.07% according to retrospectively reviewed discharge records at an US Army Medical Centre.(Kizer 2003) The prevalence of LS is probably underestimated since a third of cases are asymptomatic.(Goldstein 2005)
Age at onset
LS can occur at any age. The incidence of vulval LS increases with age, women after the menopause are most commonly affected, which may not necessarily be linked to the postmenopausal status.(Higgins 2012; Wallace 1971) A second peak is thought to occur before puberty (Tasker, McPherson 2010); both peaks are in the non-reproductive years and are associated with low oestrogen. It could be that there is a true aetiological relation which may be linked to the differences in immune responses (oestrogen favours T cell mediated rather than antibody responses). Alternatively the age distribution could be related to less lubrication allowing mechanical trauma (Köbner phenomenon). However, Wallace described a more or less continuous increase in incidence peaking around the menopause with decrease thereafter. In men the incidence seems to increase after puberty (with possibly a small prepubertal peak) and decreases again at older age (> 60 years).(Wallace 1971; Kizer 2003; Edmonds 2012) The incidence almost doubled in the third decade in one study; this may, however, be attributed to the study setting being performed at a Military Medical Centre;(Kizer 2003) but a peak around the third decade is also observed in a non-military setting.(Edmonds 2012)
Sex ratio
Women seem more affected than men, with a reported female :male ratio between 3:1 and 10:1; however, an equal gender distribution was observed in a Greek general hospital.(Wallace 1971; Meffert 1995; Leibovitz 2000; Jensen 2012; Kreuter 2013; Kyriakis 2007; Garcia-Bravo 1988; Steigleder 1976; Becker 2011)

Aetiology -Pathogenesis

The cause of LS is unknown.

Genetics

A genetic predisposition is implicated.

One study describes twice the incidence of LS in Black and Hispanic male patients compared to white patients in the US (10.59, 10.67 and 5.07 per 10,000 patients, respectively).(Kizer 2003)

Familial

A positive family history of LS is observed in 12% and 8.7% of patients with vulval LS in two British studies.(Sahn 1994; Aslaninan 2006; Sherman 2010; Higgins 2012) A Dutch cohort with genital LS shows that at least 8.6% of patients have family members with genital LS; familial occurrence is probably higher than expected and may be as high as 39%.(Aslanian; Kirtschig, abstract EADV 2014) In the Dutch study more female compared to male relatives were thought to have LS.(Aslanian; Sahn; Kirtschig, abstract EADV 2014) Genital LS is males occurs less often in families.(Edmonds 2012; Kirtschig, abstract EADV 2014) Edmonds found only 1% of their cases to have a family history of the disease.(Edmonds 2012)

HLA

Immunogenetic studies have demonstrated a significant association with the HLA class II antigen DQ7 and DRB1*12 (Marren et al) and DRB1*12 (DR12) and haplotype DRB1*12/DQB1*0301/04/09/010, and a lower frequency of DRB1*0301/04 (DR17) and haplotype DRB1*03/DQB1*02DRB1*0301/DQB1*0201/02/03 (Gao et al.) in patients compared with controls.(Marren 1995; Gao 2005) HLA-DR and DQ antigens or their haplotypes appear to be involved in both susceptibility to and protection from LS. The existence of a susceptibility gene for sclerosis in this region of the MHC is underlined by the finding that the same region is associated with an increased risk of autoimmune diseases.(Powell 2000)

LS is described to occur in individuals with **Turner syndrome** (X0 chromosome) which leads to speculations of the influence of low oestrogen in the pathogenesis.(Koupaie 1976; Lagerstedt 2013)

Gene expression pattern of LS in males using DNA microarraysunctional analysis revealed increased expression in adults and children in the immune response/cellular defence gene ontology (GO) category and reduced expression in other categories including genes related to squamous cancer. No specific HPV, autoimmune or squamous carcinogenesis-associated gene expression patterns were found. ECM1 and CABLES1 expression were significantly reduced in paediatric and adult samples respectively; the meaning of this needs further evaluation.(Edmonds Oct 2011)

In contrast, the median mRNA as well as mean protein expression of ECM proteins (e.g. proteoglycans, ECM-1) and connective tissue growth factor (CTGF) was found to be higher in vulval LS in the study by Gambichler et al. TGF-ß/Smad-3 independent up-regulation of CTGF may induce accumulation of ECM proteins and maintain fibrosis in chronic vulval LS.(Gambichler 2012)

Epigenetics refers to functionally relevant changes in the genome other than those of DNA sequence that can lead to changes in gene expression or cellular phenotype. Vulval LS is associated with altered expression of IDH enzymes and aberrant hydroxymethylation indicating an epigenetic background for the pathogenesis of vulval LS.(Gambichler 2013 oct)

Immunology

T-cells

Terlou et al. describe an autoimmune phenotype in vulval LS, characterized by increased levels of Th1-specific cytokines, a dense T-cell infiltrate, and enhanced BIC/miR-155 expression, a microRNA involved in regulation of the immune response.(Terlou 2012)

Pilatz et al. investigated the cellular composition, inflammatory infiltrate and microenvironment in boys with congenital phimosis and lichen sclerosis. They found distinct expression patterns of tissue remodeling associated genes characterized by over expression of bone morphogenetic protein 2 and its corresponding receptor, matrix metalloproteinases 1 and 9 and tissue inhibitor of metalloproteinases 1, cytokine chemokine ligands 5 (RANTES) and interleukin 4, and TGF-β2 and its corresponding receptor.(Pilatz 2013),

An interesting observation is described by Kaya et al. CD44-targeted deficiency in mouse epidermis results in LS-like histological picture.(Kaya 1997) 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 HA accumulation is a conspicuous feature.(Kaya 2000) However, increased epidermal and dermal staining in areas where there was a band of inflammatory cells but decreased in areas of sclerotic skin using a pan CD44 marker was observed by Farrell et al.(Farrell 1999)

Humoral autoimmunity

An increased incidence of autoantibodies to the extracellular matrix protein 1 (ECM1) and autoantibodies to BP180 antigen in LS are reported. This may support the idea of LS being a (humoral) autoimmune disease.(Oyama 2003; Edmonds July 2011; Howard 2004; Baldo CED 2010)
A significant interferon-gamma production was observed in response to the NC16A peptides in 6 of the 14 vulval LS patients, but not in the control subjects. There was an associated autoantibody response to BP180 in 3 LS patients with T-cell responses. These data suggest that in some vulval LS patients, NC16A domain-specific T cells circulate at sufficiently high frequency to be detectable in vitro and show rapid effector function.(Baldo JEADV 2010)
However, no increased percentage of anti-BP180 autoantibodies in LS were detected in a cohort from Greece. Authors suggest that autoantibodies in patients with genital LS represent rather an epiphenomenon than a true component of LS pathogenesis.(Patsatsi Acta Dermato Venereol in press)
Interestingly, the clinicopathological phenotype of lipoid proteinosis, which results from mutations in ECM1, resembles LS.(Oyama 2003) However, the pathogenic relevance of these findings needs further investigation.
Oxidative stress, which is involved in the pathogenesis of several autoimmune and malignant disorders, may contribute to these processes in LS.(Sander 2004) Increase of lipid peroxidation products was found within the basal cell layers of the epidermis of LS, thus co-localizing with ECM1. Oxidative DNA damage was detected throughout LS biopsies indicating that oxidative damage to lipids, DNA and proteins may contribute to sclerosis, autoimmunity and carcinogenesis in LS. The possible role of TP53 mutations in the development of vulval cancer in LS is postulated.

Disease associations

Autoimmune diseases like thyroid disease (most frequently), vitiligo, alopecia areata, autoimmune bowel disease, rheumatoid arthritis, primairy biliairy cirrhosis, pernicious anaemia, localized scleroderma/morphea, systemic lupus erythematosus, and multiple sclerosis are more frequently described in genital LS patients. These associations are more common in females (19% to 54%) than in males (3% to 5%).(Harrington 1981; Meyrick 1988; McGrath 2005; Marren 1995; Azurdia 1999; Cooper 2008; Bjekić 2011; Kreuter 2012; 2013)
However, one recent study did not confirm the association with autoimmune diseases but revealed other risk factors.(Higgins 2012)
The prevalence of **psoriasis** (Th1 response) in vulval lichen sclerosus patients was found to be higher than in the general population and among non-lichen sclerosus patients.(Eberz 2007; Simpkin 2007)
Atopic dermatitis (Th2 response) was found more commonly in boys with lichen sclerosus compared to circumcised boys without LS.(Becker 2013)
Rare associations with for example **Langerhans cell histiocytosis** are described.(Chang 2013)
Women with LS may have **other bladder, bowel and pain comorbidities**. In a series of 308 women with LS seen at a vulval clinic, self-reported conditions were overactive bladder (15.3%), stress urinary incontinence (27.9%), constipation (32.5%), irritable bowel syndrome (19.5%), thyroid dysfunction (33.1%), fibromyalgia (9.1%), temporomandibular joint disorder (13.0%) and vulvar pain (83.1%).(Berger 2012)

Trauma

The Köbner phenomenon describes the occurrence of disease specific lesions on normal appearing skin after trauma, it is described in LS. Mechanical factors like friction due to tight clothing, occlusion, surgical trauma, preputiolysis in boys, radiotherapy, and scars are thought to play an important role in triggering and maintaining LS.(Wallace 1971; Pock 1990; Tournillac 1998, Tegner 2001, Todd 2001; Gupta 2010; Villa 2012; Abdelbaky 2012)
The risk of LS was greater in parous women than nulliparous women, which may indicate that tissue damage during delivery may be a trigger.(Sider 1989; Higgins 2012)
There may be a connection to sexual abuse. In a large series of paediatric female LS, associations with

trauma, autoimmunity, and infection were noted. There was a high rate of coexisting sexual abuse with LS, possibly due to genital trauma.(Warrington 1996)
Peristomal LS is found around urostomies. It is speculate that in addition to the possible role of local trauma and occlusion, certain - as yet unidentified - constituents in the urine possibly play a role in its aetiology.(Owen 2002; Al-Niaimi 2013; Shim 2013; Bunker ACTA / BJD 2013) Bunker and co-workers emphesise the fundamental role of urine in penile LS due to microincontinence from a dysfunctional naviculomeatal valve.(Edmonds 2012)

Hormonal
The higher incidence of LS in peri- and postmenopausal women suggests a pathogenic role of sex hormones in LS. 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.(Friedrich 1984) 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.(Friedrich 1984; Neill 2002; Bracco 1993)
In normal female genitals the transition from vagina to vulva is marked by an increase in androgen receptors (AR) and a decrease in estrogen (ER) and progesterone receptors (PR). In one study 13% of LS patients showed AR staining in the parabasal cell layers of the epidermis. ER expression was present in only 1/39 and none had PR expression. Interestingly 4/5 women with ER had asymptomatic LS.(Kohlberger 1998)
Furthermore, there is evidence for the loss of AR with disease progression in both genital and extragenital skin affected by LS.(Clifton 1999; Taylor 2008) Vulval LS showed similar ERα and ERβ expression in the 'epidermal' and 'dermal' tissue layers to that of normal vulvae, whereas AR expression appeared to be absent in most cases. ER β and Ki-67 expression was correlated with ER α expression but only in the 'fibrovascular' layer of the vulva. ER α expression was absent from the 'fibromuscular' layer of diseased vulvae, while ER β expression was absent in normal tissues but was highly expressed in diseased vulvae.(Taylor 2008)
It is suggested that disturbance of the androgen dependent growth of the vulval skin by OCPs and especially by OCPs with anti-androgenic properties might trigger the early onset of LS in a subgroup of susceptible young women; 70% of LS patients vs 49% of the controls were using combinations with anti-androgenic activity (chlormadinone acetate, cyproterone acetate, dienogest, and drospirenone) in one study. Furthermore, a remission of LS after topical progesterone 8% ointment was observed when clobetasol propionate had failed.(Günthert 2008) Interestingly, progesterone only methods for contraception were also negatively associated with vulval LS.(Higgins 2012)
These findings support the influence of a hormonal pathogenesis in LS; this may be significant in the treatment of the disease.

Infectious
An infective aetiology, e.g. *Borrelia burgdorferi* or a human papilloma virus, has been postulated but there are no clear data showing that LS is related to an infection.(Lau 1995; Nasca 2006; Nieuwenhof HP van 2009, Gambichler 2009; Edmonds 2009; Alonso-Llamazares 1997) There are sporadic reports of LS associated with a hepatitis C infection.(Shim 2012; Yashar 2004; Boulinguez 1997)

Drugs
There are hardly any reports on the induction of LS by drugs. LS after carbamazepine treatment for epilepsy in a male patient and imatinib mesylate for chronic myelogenous leukemia in a female are described.(Pranteda 2013; Skupsky 2010) Imatinib specifically inhibits the activity of tyrosinkinase ABL in diseased cells inhibiting their proliferation. It is being investigated for use in the treatment of sclerosing dermatoses. It is also described to induce lichen planus.
An inverse relationship between the presence of vulval LS and use of beta-blockers and ACE inhibitors is described. ACE inhibitors may diminish the inflammatory process; the possible mechanism of action of beta-blockers relies on blocking cyclic AMP levels, resulting in upregulation of keratinocyte proliferation, and reduced differentiation and increased motility of lymphocytes.(Baldo 2014)

Risk factors / Trigger

Increased risk of LS is described in:

- Parous women compared to nulliparous women (Sideri 1989; Tang 2003)
    - Finding not significant when only married women were considered (Sideri)
- OCPs with anti-androgenic properties (Günthert 2008)
- Family history of diabetes mellitus (Higgins 2012)
- Pelvic surgery (Higgins 2012)
- Hot food (Tang 2003)
- Vulvitis and urethritis (Tang 2003)
    - Vulval infections not confirmed (Higgins 2012)
- Atopic dermatitis in boys (Th2 response)(Becker 2013)
- Fitzpatrick phototype 1 and 2 in boys (Villa 2012)
- Maneuvers of "mechanical reduction of the foreskin" (MRF) performed at least 5-10 times per month (Villa 2012)

Reduced risk of vulval LS:

- Intake of carotenoids was inversely associated with vulval lichen sclerosus (Sideri)
- Use of barrier methods for contraception (less risk of infections?) (Higgins 2012)
- Progesterone only methods of contraception (Higgins 2012)
- Hormone replacement therapy (Higgins 2012)
- Hayfever (Th2 response) (Higgins 2012)

No difference was observed in the distribution of cases and controls with reference to education, smoking habits, body mass index, and previous history of diabetes or retinoids and risk of vulval lichen sclerosus.(Sideri; Higgins 2012)

Cancer development

Squamous cell carcinoma (SCC) has been described in association with female and male genital LS. It is not associated with extragenital LS. Less commonly verrucous carcinoma which seems to be associated particularly with vulval LS (Wang 2010), in addition melanoma, basal cell carcinoma or Merkel cell carcinoma are reported, but no studies suggest that there is an increased frequency of these tumours.

The risk of the development of genital SCC in patients with LS is estimated to be 4% to 5% over a lifetime (Wallace 1971; Pugliese 2007; Nasca 1999), which is probably an overestimation; it may even be lower in hypertrophic LS.(Weyers 2013) In a 10-year multicentre cohort of 130 male patients with genital LS, histological changes of SCC were found in eight, verrucous carcinoma in two and erythroplasia of Queyrat (in situ SCC) in one.(Barbagli 2006) The background incidence of vulval SCC in the UK population is 2/100,000.(CRUK 2010) Penile cancers in Europe and the United States account for less than 0.5% of all male cancers; they are mostly SCCs.

Worldwide about 50% of penile and vulval carcinomas are induced by transforming HPV infections with high-risk genotypes. The remaining cancers develop in the absence of HPV, often in the background of chronic inflammatory skin diseases like LS and LP.(Mannweiler 2013; Regauer 2012; vd Nieuwenhof 2009)

Therefore, a dual pathway of vulval and penile cancer development is postulated: HPV-induced=VIN / high-grade intraepithelial lesion and HPV negative=differentiated VIN.(vd Nieuwenhof 2009; Mannweiler 2013) Cancer in LS and LP seems to develop via differentiated VIN to SCC.(Mannweiler 2013; Reyes 2014) The classification is made histologically and immunohistologically; the HPV status needs to be determined.

Altered expression of p53 oncogene, chronic inflammation, and oxidative stress are postulated to induce malignant transformation in patients with genital LS.(Wang 2010; Sander 2004) Mutations were detected in 103 of 349 assays and consisted of KRAS G34A, G34T, G35A, and TP53 C742T, G818C, C817T, and G818A mutations. Mutant prevalence varied from 1 to 20 per 10(6) wild-type cells. Mutations occurred significantly more frequently in LS (78/224 (35%)) than adjacent normal (20/88 (23%)) and non-adjacent normal genital skin (5/38 (13%)). KRAS G34A mutation was relatively

common to all classes of specimen, whereas TP53 gene C742T and G818C mutations were significantly more frequent in LS than normal genital skin. In matched samples, immunohistochemistry evaluation of p53 protein expression revealed the presence of epidermal p53 clones in LS whose presence and number significantly correlated with the presence of TP53 C742T and G818C mutations. Based on these results, it appears oncogenic point mutations occur in normal genital skin, and are selected for in LS.(Tapp 2007) Furthermore, HPV-negative cancers associated with dermatoses like LS and LP express p53, but lack $p16^{ink4a}$ overexpression; further protein markers are sought to detect malignant transformation in LS early.(Mannweiler 2013; Guerrero-Setas 2013; Carlson 2013)
Treatment with very potent topical steroids improves symptoms of LS. It is not known if well treated LS is less likely to develop malignancies or if the contrary is the case as local immunosuppression will increase the risk of malignancies.(Renaud-Vilmer 2004; Jones 2004; Carli 1995)
There is accumulating evidence of an increased risk of anogenital cancer in familial LS.(Sherman 2010; Kirtschig, abstract EADV 2014) This may point towards a genetic background of cancer development in familial LS which may justify family screening for LS to help select patients who need long term follow-up in order to detect anogenital carcinoma early.

Social / Sexual impact
Lichen sclerosus has a huge impact on the quality of life. The majority of women and men of all ages report that LS has a detrimental effect on sexual life, with problems including dyspareunia, apareunia and difficulty achieving orgasm. The symptoms may relate to continuing inflammatory disease as well as to anatomic changes and scarring from long-standing active disease.(Dalziel 1995; Edmonds 2011) Many affected people feel embarrassed; some have persistent itch and pain despite successful control of the inflammation, and many are concerned about how the disorder may progress. This affects daily private life and work.

Course of disease with or without treatment
LS usually runs a chronic course. The number of spontaneous remissions, in particular in early and mild cases is unknown as these individuals may not present to a physician. Once patients consult a physician and are diagnosed with LS the course is usually chronic. Treatment is reported to suppress symptoms like pruritus in 80 to 90% of female patients.(Cooper 2004) Scarring is, however, irreversible and it is not known if early treatment will prevent scarring (men respond better to early treatment).
Follow-up in particular in troublesome LS is recommended but may not be preformed appropriately.(Balasubramaniam 2007) Ideal intervals in order to detect e.g., cancer development early are unknown.
Men and boys seem to benefit more from early treatment with potent topical steroids or circumcision, cure is expected in about 50% and nearly 100% after treatment respectively.(Edmonds 2011, Becker 2011)
The course of LS in girls is still a matter of debate; spontaneous remission during puberty is discussed but there is accumulating evidence that a definite remission may not occur, at least not in the majority of cases.(Powell 2002) However, penile LS in boys is responsive to potentent topical steroids (41%) or circumcision in nearly 100% of reported cases.(Kiss 2005, Becker 2011)
The ideal long-term maintenance treatment is not established as this requires follow-up studies for many years which are difficult to perform.

Course during pregnancy
There are hardly any reports on LS during pregnancy.(Higgins 2012; Günthert 2008; Kirtschig unpublished data) Günthert et al. describe that in one study 4/40 patients with LS became pregnant during the first 6 months after referral and showed complete remission of LS during pregnancy. After 6 months of initial treatment and/or change/ stoppping of oral contraception all patients were without symptoms and showed good resolution of morphological changes.(Günthert 2008)
Unpublished data support the observation that LS is often less troublesome during pregnancy (9/18) compared to disease activity before and after delivery.(Kirtschig unpublished data)
Women are reluctant to use topical steroids during pregnancy and the risk of growth retardation

with use of ultra-potent topical steroids exists.(Mahé 2007; Chi 2009 / 2013) In 5/18 pregnancies women used very potent topical steroids about once every second week and delivered healthy children, that were not small for gestation. The majority had vaginal deliveries (14/18), 3 cesarean sections (bradycardia of the unborn), and 2 had not delivered at the time. Of the 14 vaginal deliveries 5 ruptured (3 women), there were 6 episiotomies one of which had problems with healing.(Kirtschig unpublished data) Higgins et al. also report no problems with perineal suturing or healing post-delivery.(Higgins 2012)

Who takes care of patients with LS?

Dermatologists
Andrologists
Genitourinary Medicine
Gynaecologists
Paediatricians
Urologists
Paediatric surgeons
General practicioners
Genito urinary physicians/sexual health physicians

What is the current treatment of choice?

Topical application of potent or ultra-potent steroids such as clobetasol propionate 0.05% cream or preferably ointment has been shown to be safe and effective in treating both women and men and is recommended in many guidelines.(Chi 2011; Neill) The frequency of application and maintenance treatment is a matter of debate, a common practice is to use clobetasol propionate once or twice daily for 3 months, with a possible reduction of application frequency after one month, and then as required. It has also been found to be effective in children. Thinning and erythema of the skin may occur, in particular in children, but resolves quickly when treatment is interrupted.

Clearence of LS after circumcision in males with mild to intermediate disease is described in the majority of cases (cure claimed in nearly 100%).(Meuli 1994; Depasquale 2000; Mattioli 2002; Kiss 2005, Becker 2011; Edmonds 2012) However, there are no randomized controlled trials confirming this and good long-term studies are lacking. Conservative treatment is often performed first (in particular by non-surgical specialties) and may lead to clearance in more than half of the treated patients.(Edmonds 2012) In order to achieve clearance and maintain it, any sort of triggering factors need to be avoided (see details below).

Interest has been shown in the topical calcineurin inhibitors tacrolimus and pimecrolimus.(Hengge 2006; Goldstein 2011) One RCT found no differences between pimecrolimus and clobetasol propionate in relieving the symptoms of pruritus and burning/pain. However, pimecrolimus was less effective than clobetasol propionate with regard to the 'investigator-rated global degree of improvement'. There is a theoretical risk of the development of malignancies, as one study has shown an increase in tumours in mice infected with herpes and treated with systemic tacrolimus.(Mistrikova 1999)

No significant benefit for topical testosterone, dihydrotestosterone, and progesterone is demonstrated in randomized controlled trials; however, treatment with progesterone is being further investigated in an ongoing RCT.(Günthert)

Retinoids used orally and topically can be irritant, but improvement has been shown.(Virgili 1995; Bousema 1994) Other systemic treatments, UV light and surgical interventions are tried but their effects have not been evaluated in a systematic fashion.

LS is a Th-1 mediated disease. This means that treatments that interfere with e.g. interferon gamma or TNF alpha may be potential treatment options for LS; comparable to treatments for psoriasis. Systemic treatments have rarely been used in vulval LS, however, in severe cases systemic treatment with systemic steroids, fumarates, MTX or ciclosporin may be justified. Theoretically anti-TNF acting biolgics may be effective; however, an unpublished observation describes development of LS in two patients treated with infliximab.(Wojnarowska F)

Another interesting option may be the PDE-antagonist Apremilast (PDE = phosphodiesterase which breaks down cAMP). Cell activity inhibition with a PDE-antagonist will increase cAMP in cells and will

inhibit TNF-alpha production, comparable to Pentoxyfylline (Trental). However, Pentoxyfylline in contrast to Apremilast is not very specific for T-cells and is accompanied by many adverse effects.

Treatment preference may vary between specialties. A Dutch study compared the treatment and follow-up of patients with LS at the departments of Gynaecology and Dermatology. At the Gynaecology department, LS patients more often received surgical treatment, topical estrogens, and lidocaine ointment, whereas at the Dermatology department, potent and very potent topical corticosteroids were more often prescribed. Follow-up frequencies were similar in both specialties and took place at 3 to 4 visits in the first year and at least once a year afterward. One patient developed vulvar squamous cell carcinoma. This patient had withdrawn from follow-up and had her carcinoma diagnosed 74 months after the LS had been diagnosed.(Avoort vd 2010)

Interventions

Topical Treatment

Topical Glucocorticosteroids
Topical corticosteroids are the mainstay of treatments for LS in females.

Women/girls
Topical clobetasol propionate is the gold standard treatment for vulval LS in women and girls, and dermatologists have been using it for over two decades.(Dalziel 1991; Dalziel 1993) A placebo-controlled RCT evaluated the efficacy of topical clobetasol propionate in treating vulval LS in women after three months' application (1 month twice daily, 2 months once daily), and found clobetasol propionate significantly improve the symptoms and signs (75%) rated by either the participants or investigators.(Bracco 1993) Also, the trial found no adverse events (e.g. predisposition to infection, worsening of skin atrophy, and contact dermatitis) in either the clobetasol propionate or placebo group. Topical clobetasol propionate 0.05% ointment (CP) was compared with mometasone furoate (MMF) 0.1% ointment in a RCT of 54 women with vulval LS. By the end of the 12 weeks, 24 (88.9%) patients of the clobetasol propionate group and 24 (88.9%) of the MMF group responded according to the criteria; 59.3% and 37% of patients in the CP group and 66.7% and 48.2% in the MMF group achieved an improvement of at least 75% in subjective and objective scores, respectively. The decrease in mean symptom and sign scores was significant compared to baseline with both treatments. No significant differences were found in any of the assessed efficacy endpoints between CP and MMF. Both treatments were well tolerated.(Virgili 2014; Virgili JEADV 2013)
A case series showed 6-8 week's application of clobetasol propionate effective in treating vulval LS in girls.(Garzon 1999) A case series of 15 prepubertal girls showed clobetasol propionate was effective in treating vulval LS and the complications of treatment were infrequent, minor, and easy to manage.(Smith 2001) This is confirmed by an unpublished case series of girls with vulval LS by Powell et al. About 70% of the girls treated with clobetasol propionate 0.05% ointment or cream daily for two to three months achieved a remission of symptoms and signs (improvement in all), 55% requiring no further treatment. Patients treated with mild steroids showed improvement in all but about two thirds of the patients required continuous treatment after the initial course.(Powell unpublished data)
Next to a RCT are less potent topical steroids (mometasone furoate, triamcinolone, prednicarbate) shown to be effective in treating vulval LS in uncontrolled studies.(Virgili 2014, Virgili JEADV 2013, Le Fevre 2010, Lopez-Olmos 2003)

Men/boys
Both mometasone furoate 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 mometasone furoate 0.05 ointment in treating penile LS in 40 boys after five weeks' application.(Kiss 2001) Mometasone furoate was found to improve the clinical grade of phimosis in 7/17 boys (41%) after 5 weeks treatment; no improvement was seen in late disease (the treatment was not curative, 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; but LS was not proven histologically.(Vincent 2005)
A retrospective study in 21 men with penile LS found clobetasol dipropionate 0.05% cream effective and safe after 7 weeks treatment in average in 16/21 (76%) (6 required circumcision) with no risk of epidermal atrophy.(Dahlman-Ghozlan 1999) 185 males treated with clobetasol propionate 0.05% (for about 12 weeks with decreasing frequency) were analyzed retrospectively, 60% were successfully treated, with a relaps in some reducing it to 50% success rate, the mean follow-up was 15 months.(Edmonds 2012)

Long-term
Long-term use of either very potent or moderate topical corticosteroids appears to be effective and safe. A RCT of 25 patients with vulval LS revealed that proactive maintenance therapy with twice-weekly application of mometasone furoate 0.1% ointment was effective and safe in maintaining remission (7/8 steroid group, 3/9 vitamin E group, 3/8 cold cream group).(Virgili BJD 2013) A retrospective study (Dalziel 1991 & 1993) found long-term remission of vulval LS with mild to moderate topical corticosteroid treatment (including clobetasone butyrate 0.05% & hydrocortisone 1%) following an initial 12-week treatment with clobetasol propionate 0.05% cream twice daily. A retrospective study showed 6 months' use of clobetasol propionate 0.05% on a regular basis appears to be safe and effective in treating severe vulval LS in postmenopausal women, but the improvement was observed mainly on the symptoms and less on the signs.(Diakomanolis 2002) A retrospective study with a mean follow-up of 66 months in 74 girls and 253 women found an excellent response to ultrapotent topical corticosteroids, relieving symptoms in most and completely reversing the skin changes in approximately one fifth (20%) of affected patients after 66 months in average.(Cooper 2004) A prospective study with a median follow-up of 4.7 years in 83 women with vulval LS found clobetasol propionate effective and the remission rate was associated with younger age, with fewer remissions in older women (the estimated incidence of remission at 3 years being 72% in women younger than 50 years, 23% in women aged between 50 and 70 years, and 0% in women older than 70 years).(Renaud-Vilmer 2004) A retrospective study with a mean follow-up duration of 6.2 years found long-term treatment of adult vulval LS with individualised regimes using moderate potency topical corticosteroid safe and effective.(Bradford 2010)

Bracco GL, Carli P, Sonni L, et al. Clinical and histologic effects of topical treatments of vulval lichen sclerosus. A critical evaluation. Journal of Reproductive Medicine 1993;38:37-40.

Bradford J and Fischer G. Long-term management of vulval lichen sclerosus in adult women. Australian & New Zealand Journal of Obstetrics & Gynaecology 2010;50:148-52.

Cooper S, Gao XH, Powell JJ, Wojnarowska F. Does treatment of vulvar lichen sclerosus influence its prognosis? Arch Dermatol 2004;140:702-6.

Dalziel KL, Wojnarowska F. Long-term control of vulval lichen sclerosus after treatment with a potent topical steroid cream. Journal of Reproductive Medicine 1993;38:25-7.

Dalziel KL, Millard PR, Wojnarowska F. The treatment of vulval lichen sclerosus with a very potent topical steroid (clobetasol propionate 0.05%) cream. Br J Dermatol 1991;124:461-4.

Diakomanolis ES, Haidopoulos D, Syndos M, et al. Vulvar lichen sclerosus in postmenopausal women: a comparative study for treating advanced disease with clobetasol propionate 0.05%. Eur J Gynaecol Oncol 2002;23:519-22.

Edmonds EV, Hunt S, Hawkins D, et al. Clinical parameters in male genital lichen sclerosus: a case series of 329 patients. J Eur Acad Dermatol Venereol. 2012;26:730-7

Garzon MC, Paller AS. Ultrapotent topical corticosteroid treatment of childhood genital lichen sclerosus. Arch Dermatol 1999;135:525-8.

Kiss A, Csontai A, Pirot L, Nyirady P, Merksz M, Kiraly L. The response of balanitis xerotica obliterans to local steroid application compared with placebo in children. Journal of Urology 200;165:219-20.

LeFevre C, Hoffstetter S, Meyer S, Gavard J. Management of lichen sclerosus with triamcinolone ointment: effectiveness in reduction of patient symptom scores. J Low Genit Tract Dis 2011;15:205-9.

Lopez-Olmos J. Clobetasol versus prednicarbate in the treatment of vulvar pruritus, with or without dystrophy. [Spanish] Comparacion de clobetasol frente a prednicarbato para el tratamiento del

prurito vulvar con o sin distrofia. Clinica e Investigacion en Ginecologia y Obstetricia 2003;30:117-25.
Renaud-Vilmer C, Cavelier-Balloy B, Porcher R, Dubertret L. Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease. Arch Dermatol 2004;140:709-12.
Smith YR, Quint EH. Clobetasol propionate in the treatment of premenarchal vulvar lichen sclerosus. Obstetrics & Gynecology, 2001;98:588-91.
Vincent MV, Mackinnon E. The response of clinical balanitis xerotica obliterans to the application of topical steroid-based creams. Journal of Pediatric Surgery 2005;40:709-12.
Virgili A, Minghetti S, Borghi A, Corazza M. Proactive maintenance therapy with a topical corticosteroid for vulvar lichen sclerosus: preliminary results of a randomized study. Br J Dermatol 2013;168:1316-24.
Virgili A, Borghi A, Minghetti S, Corazza M. Mometasone fuoroate 0.1% ointment in the treatment of vulvar lichen sclerosus: a study of efficacy and safety on a large cohort of patients. J Eur Acad Dermatol Venereol. 2013;23:189-94.
Virgili A, Borghi A, Toni G, Minghetti S, Corazza M. First randomized trial on clobetasol propionate and mometasone furoate in the treatment of vulvar lichen sclerosus: results of efficacy and tolerability. Br J Dermatol 2014 Feb. [Epub ahead of print]

Very potent or potent topical corticosteroids are effective in treating genital LS. Proactive maintenance treatment may be considered to maintain remission, often required in females. Long-term use of very potent or potent topical corticosteroids appears effective and safe if needed (in active disease); this refers in particular to treatment in females as male genital LS is aimed to be treated curatively in most cases.
Evidence level: 1 to 2
Recommendation grade: A

Glucocorticosteroids

Injections

The aim of a long-term study was to quantify the reduction of pruritus, active disease progression, and cessation of scarring after subdermal steroid injections for histologically proven LS that responded poorly to topical steroids. The injections were given each month until the patients were free of pruritus and demonstrated no progression of the LS. Follow-up injections occurred at 2-month intervals as maintenance therapy. An intermittent application of topical triamcinolone daily for 2–3 days was allowed for intermittent pruritus between the injections. Skin turgor, elasticity, stretchiness, scar formation and the anatomy of the vulva was assessed for the presence of anatomical distortion. LS was defined as advanced when sexual intercourse was difficult, impossible, and/or painful because of the vulvar scarring or introital constriction severe enough to interfere with the outflow of urine, or scaring resulted in fissuring secondary to physiologic stretching (e.g., bowel movements). The primary outcome was to quantify the number and intervals of steroid injections required to obtain the cessation of active disease progression and symptoms of itching and pain using a clinical chart review of 88 patients. 62 patients (72.9%) had a reduction of disease progression at 60 months follow-up, in 10 patients (11.8%), the disease remained stable and in 13 patients (15.3%) the disease continued to progress. 72/88 patients (81.8%) had no more pruritus after 4 injections; however, 31 of those patients (35.2%) required intermittent topical triamcinolone for pruritus relief in between monthly injections. Injections every other month or less were required to prevent relapses in all patients. The conclusion was that the majority of the patients with advanced symptomatic vulvar LS obtained rapid relief of pruritus after monthly subdermal steroid injections. Maintenance treatment was required to control pruritus, to prevent disease progression, and subsequent additional vulvar scarring.(Baggish 2006)

Patients with vulval pruritus diagnosed with vulval LS and squamous hyperplasia of duration greater than 6 months were studied. Fifty eight patients (number of LS unknown) were randomly divided; the treatment group (28) was injected with 50 mg triamcinolone only once and a control group (30) was injected with 5 mg triamcinolone each week for 4 to 6 weeks. There was a decrease in severity scores for both symptoms (increased with higher doses) and physical findings. A decrease in severity scores on histopathology was observed in 10 patients who were biopsied.(Ma 2010)

In an open trial 8 patients with LS who could not use primary topical treatments received intralesional injections of triamcinolone. There was a decrease in severity scores for symptoms and physical findings. In four patients who consented to post-treatment biopsy, there was a decrease in severity scores on histopathological findings. Intralesional injection of triamcinolone hexacetonide into sites of vulval lichen sclerosus seems to be an effective alternative to topical agents.(Mazdisnian)
Between 2002 and 2007, boys requiring surgery for balanitis xerotica obliterans (BXO) were offered either foreskin preputioplasty or primary circumcision. The preputioplasty technique involved triradiate preputial incisions and injection of triamcinolone intralesionally. 104 boys opted for foreskin preputioplasty, and 32, for circumcision. At a median follow-up of 14 months (interquartile range, 2.5-17.8), 84 (81%) of 104 in the preputioplasty group had a fully retractile and no macroscopic evidence of BXO. Of 104, 14 (13%) developed recurrent symptoms/BXO requiring circumcision or repeat foreskin preputioplasty. The incidence of meatal stenosis was significantly less in the foreskin preputioplasty group, 6 (6%) of 104 vs 6 (19%) of 32 (p = 0.034). Results show a good outcome for most boys undergoing foreskin preputioplasty and intralesional triamcinolone for BXO. There is a small risk of recurrent BXO, but rates of meatal stenosis may be reduced.(Wilkinson)

Baggish MS & Ventolini G. Lichen sclerosus: Subdermal steroid injection therapy. A large, long-term follow-up study. Journal of Gynecologic Surgery 2006;22:137-141.

Ma D & Yuan JH. Application of subcutaneous injection of large dose of triamcinolone acetonide (TA) in the treatment of vulvar lichen sclerosus and squamous hyperplasia. [Chinese]. Journal of Dalian Medical University 2010;32:83-85.

Mazdisnian F, Degregorio F, Palmieri A. Intralesional injection of triamcinolone in the treatment of lichen sclerosus. J Reprod Med 1999;44:332-4.

Wilkinson DJ, Lansdale N, Everitt LH, et al. Foreskin preputioplasty and intralesional triamcinolone: a valid alternative to circumcision for balanitisxeroticaobliterans. J Pediatr Surg 2012;47:756-9.

The positive effect on pruritus, physical signs like disease progression and scarring by intralesional triamcinolone acetonide injections (e.g. 50mg) or a solution containing 2 mg of dexamethasone in vulval, penile and oral LS (one case) is shown in few case series and one small RCT (vulva). Steroid injections may be a treatment option for patients with treatment resistant itch or who are unable to apply topical steroids.
Evidence level: 1+
Recommendation grade: B

Topical sex hormones

Topical Oestrogens

Topical oestrogens are a treatment of postmenopausal vaginal atrophy in some women.(Michalas) This is a well-established treatment in the oestrogen deficient postmenopausal situation causing 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, though both conditions may occur simultaneously. The vulva itself has few oestrogen receptors which however may be up-regulated in some situations.(Hodgins 1998)
There is one randomized multicentre study comparing oestrogen 0.1% cream with testosterone propionate 2% cream in 64 patients with “vulval dystrophy”.(Seidelmann 1993) Neither the age nor a histological diagnosis is provided, perianal involvement is mentioned which points towards a diagnosis of LS rather than an oestrogen deficiency. 23 patients in the testosterone group reported androgenizing adverse effects; 3 hours after the application of 20 mg testosterone serum levels of testosterone propionate between 0.12 and 0.65ng/ml, comparable to levels in fertile men, were observed. Treatment effects were comparable between the groups but are not detailed! The authors recommend treatment with oestrogens rather than testosterone because of the adverse effects.

Seidelmann I, Strecker JR. Comparative studies on the efficacy of a testosterone propionate cream and an estriol cream in the treatment of vulva dystrophy.[German] Vergleichende Untersuchungen zur Wirksamkeit einer Testosteronpropionat-Creme mit einer Estriol-Creme bei der Behandlung der Vulvadystrophie. Archives of Gynecology and Obstetrics 1993; 254(1-4):304-305.

Michalas S, Papandrikos A, Koutselini E, Tzingounis V. Local therapy of atrophic vaginal conditions with oestriol suppositories. Journal of International Medical Research 1980;8:358-60.

It is not clear as to whether the above mentioned study investigated topical oestrogens in patients with LS. Topical oestrogens for the treatment of LS alone cannot be recommended

Topical Testosterone

In the past 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.(Friedrich 1984; Neill 2002; Bracco 1993). 5 RCTs are published that compare testosterone with other treatments.

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.(Bracco 1993; Sideri 1994)

A very small cross-over trial on dihydrotestosterone vs placebo found no significant efficacy in either participant-rated improvement of symptoms or investigator-rated improvement of gross appearance.(Paslin 1991)

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 [adverse drug reactions that were severe enough to require withdrawal of treatment / adverse drug reactions that were not severe enough to require cessation of treatment].(Bracco 1993)

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].(Paslin 1996)

One small study found, when used as maintenance therapy, that testosterone worsened the symptoms ($p < 0.05$) while the vehicle-based placebo caused no change in symptoms or gross appearance. No significant differences in adverse drug reactions between testosterone and placebo were found.(Cattaneo 1996)

Bracco GL, Carli P, Sonni L, Maestrini G, De Marco A, Taddei GL, et al. Clinical and histologic effects of topical treatments of vulval lichen sclerosus. A critical evaluation. Journal of Reproductive Medicine 1993;38:37-40.

Cattaneo A, De Marco A, Sonni L, Bracco GL, Carli P, Taddei GL. Clobetasol vs. testosterone in the treatment of lichen sclerosus of the vulvar region [Clobetasolo vs testosterone nel trattamento del lichen scleroso della regione vulvare]. Minerva Ginecologica 1992;44(11):567-71.

Cattaneo A, Carli P, De Marco A, Sonni L, Bracco G, De Magnis A, et al. Testosterone maintenance therapy. Effects on vulvar lichen sclerosus treated with clobetasol propionate. Journal of Reproductive Medicine 1996;41:99-102.

Paslin D. Treatment of lichen sclerosus with topical dihydrotestosterone. Obstetrics & Gynecology 1991;78:1046-9.

Paslin D. Androgens in the topical treatment of lichen sclerosus. International Journal of Dermatology 1996;35:298-301.

Sideri M, Origoni M, Spinaci L, Ferrari A. Topical testosterone in the treatment of vulvar lichen sclerosus. International Journal of Gynaecology & Obstetrics 1994;46:53-6.

The data from RCTs found no significant benefit for topical testosterone and dihydrotestosterone in the treatment of vulval LS when compared with topical clobetasol propionate 0.05%. When used as maintenance therapy after an initial treatment with topical clobetasol propionate in another trial, topical testosterone worsened the symptoms ($p < 0.05$).

Evidence level: 1+

Recommendation grade: A

Summary

Treatment of LS with topical testosterone cannot be recommended.

Topical Progesterone

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].(Bracco 1993) A pilot studies suggests that topical progesterone is effective in the treatment of early onset LS in young women when used in a concentration of 8%.(Günthert 2008)
Results of an RCT of 62 patients with vulval LS comparing progesterone 8% vs clobetasol propionate 0.05% for 12 weeks are awaited in the end of 2014.(Günthert)
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, 5 patients had some benefit, and 5 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.(Leone 1993)
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. Lichen sclerosus as such persisted.(Parks 1990)

Bracco GL, Carli P, Sonni L, et al. Clinical and histologic effects of topical treatments of vulval lichen sclerosus. A critical evaluation. Journal of Reproductive Medicine 1993;38(1):37-40.
Leone M, Gerbaldo D, Caldana A, Leone MM and Capitanio GL. Progesterone topically administered influences epidermal growth factor immunoreactivity in vulvar tissue from patients with lichen sclerosus. Cervix and the Lower Female Genital Tract 1993;11:25-27.
Günthert AR, Faber M, Knappe G, et al. Early onset vulvar Lichen Sclerosus in premenopausal women and oral contraceptives. European Journal of Obstetrics, Gynecology, & Reproductive Biology 2008;137:56-60
Parks G, Growdon WA, Mason GD, et al. Childhood anogenital lichen sclerosus. A case report. J Reprod Med 1990;35:191-3.

There is no significant efficacy of progesterone 2% cream in the treatment of LS when compared to topical clobetasol propionate 0.05%. A pilot study suggests that progesterone used in a concentration of 8% may be more effective; results of a RCT are awaited.
Evidence level: 1+
Recommendation grade: A

Summary
Topical progesterone 2% has not shown to be very effective and is not superior to topical clobetasol propionate in the treatment of LS.

Topical calcineurin inhibitors / Non-antibiotic macrolides

Topical Ciclosporin
A study by Carli et al. included five adult women with histologically proven untreated LS. After 8 weeks treatment with ciclosporin a significant improvement of symptoms was reported by one patient, three reported slight improvement, one no changes. Complete recovery was not found in any patient.(Carli 1992) Based on the limited data, the therapeutic efficacy of topical ciclosporin cannot be determined.(Echalal 1995, Chi 2010)

Carli P, Cattaneo A, Taddei G, Giannotti B. Topical cyclosporin in the treatment of vulvar lichen sclerosus: clinical, histologic, and immunohistochemical findings. Arch Dermatol 1992;128:1548-9.
Elchalal U, Gilead L, Vardy DA, et al. Treatment of vulvar lichen sclerosus in the elderly: An update. Obstetrical and Gynecological Survey 1995;50:155-162.
Chi C-C, Kirtschig G, Baldo M, Brackenbury F, Lewis F, Wojnarowska F. Topical interventions for genital lichen sclerosus. Cochrane Database of Systematic Reviews 2010 , Issue 1

Topical ciclosporin may be effective in a minority of LS patients; it cannot be recommended for the treatment of LS.
Evidence level: 3
Recommendation grade: D

Tacrolimus
The efficacy and safety of topical tacrolimus in the treatment of LS is reported in several case series but no comparative randomized studies are available.

A multicentre, phase II trial assessed the safety and efficacy of tacrolimus ointment 0.1% for the treatment of LS.(Hengge 2006) Eighty- four patients (49 women, 32 men and 3 girls) between 5 and 85 years with long-standing, active LS (79 with anogenital and 5 with extragenital LS) were treated twice daily for 16 weeks. 14 dropped out early (surgery in 8 men?). 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. Transient burning and itching during the first couple of days of treatment were the two most common adverse effects. Infections such as genital herpes and vulvovaginal candidiasis both occurred in 2% of patients. No malignancy was observed during an 18-month follow-up period.

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%.(Virgili 2007)

Sotiriou et al. treated 10 postmenopausal women with biopsy-proven recalcitrant vulval LS with tacrolimus ointment 0.1% twice daily for 8 weeks. Drug-related side effects described as a burning sensation at the point of application occurred in 4 patients within the first week of treatment. Reactions were mild and transient. 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.(Sotiriou)

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 acetonite 0.1% cream or tacrolimus 0.1% ointment suggests that there is no difference between the two in preventing the relapses. Treatment of extragenital LS with tacrolimus combined with UV light was used in few patients successfully.(Kyriakou; Kim; Valdivielso-Ramos)

Lichen sclerosus predisposes to the occurrence of malignancies (squamous cell carcinoma), even in the natural course of the disease.(Goldstein 2009, Wallace) The effect of the long-term use of topical calcinurininhibitors with respect to the development of malignancies is not known.(Spergel) Although a causal relationship has not been established, rare cases of skin malignancies and lymphoma have been reported in patients treated with these agents.(Spergel; Langeland 2005) However, there is no evidence of systemic immune suppression or increased risk of malignancies in patients treated intermittently with topical pimecrolimus or tacrolimus in clinical trials followed-up for up to 4 years. The observed incidence of malignancies in post-marketing surveillance is lower than that detected in the general population.(Spergel; Langley; Hultsch) None of the case reports and initial studies mentioned have described the occurrence of skin malignancies or lymphomas in patients with anogenital lichen sclerosus treated continuously with pimecrolimus cream 1% or tacrolimus ointment for long periods of time, but these preliminary data need to be confirmed by controlled long-term trials.(Goldstein 2009)

Goldstein AT, Thac D, Luger T. Topical calcineurin inhibitors for the treatment of vulvar dermatoses. European Journal of Obstetrics & Gynecology and Reproductive Biology 2009;146:22–29

Hengge UR, Krause W, Hofmann H, et al. Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus. Br J Dermatol 2006;155:1021-8.

Hultsch T, Kapp A, Spergel J. Immunomodulation and safety of topical calcineurin inhibitors for the treatment of atopic dermatitis. Dermatology 2005;211:174–87.

Kim GW, Park HJ, Kim HS, Kim SH, Ko HC, Kim BS, Kim MB. Topical tacrolimus ointment for the treatment of lichen sclerosus, comparing genital and extragenital involvement. J Dermatol 2012;39:145-50.

Kyriakou A, Patsialas C, Patsatsi A, Sotiriadis D. Treatment of male genital lichen sclerosus with clobetasol propionate and maintenance with either methylprednisolone aceponate or tacrolimus: a retrospective study.J Dermatolog Treat 2013 May 6.

Langeland T, Engh V. Topical use of tacrolimus and squamous cell carcinoma on the penis. Br J Dermato 2005;152:183-5.

Langley RGB, Luger TA, Cork MJ, Schneider D, Paul C. An update on the safety and tolerability of pimecrolimus cream 1%: evidence from clinical trials and post-marketing surveillance. Dermatology 2007;215:27–44.

Sotiriou E, Apalla Z, Patsatsi A, Panagiotidou D. Topical tacrolimus for recalcitrant vulvar lichen sclerosus. Eur J Dermatol 2009;19:515-6.
Spergel JM, Leung DY. Safety of topical calcineurin inhibitors in atopic dermatitis: evaluation of the evidence. Curr Allergy Asthma Rep 2006;6:270–4.
Valdivielso-Ramos M, Bueno C, Hernanz JM. Significant improvement in extensive lichen sclerosus with tacrolimus ointment and PUVA. Am J ClinDermatol 2008;9:175-9.
Virgili A, Lauriola MM, Mantovani L, Corazza M. Vulvar lichen sclerosus: 11 Women treated with tacrolimus 0.1% ointment. Acta Dermato Venereol 2007;87:69-72.

Topical tacrolimus may be an effective and probably safe alternative for the treatment of LS in some patients. Potent topical corticosteroids seem more effective.
Evidence level: 2+
Recommendation grade: C

Tacrolimus in Children

There are few case series reporting of the treatment of LS with topical tacrolimus in children. Three pre-pubertal girls and 3 adults were treated with 0.1% tacrolimus ointment once daily. All patients experienced complete resolution with long-lasting remission for up to 1 year. No major adverse effects were observed, and treatment was well tolerated. A major advantage over topical corticosteroids is the lack of skin atrophy.(Böhm) 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 without side effects.(Matsumoto) 14 prepubertal girls (4 to 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. No severe side effects were observed.(Li 2013) However, it has been hypothesized that the immunosuppressive effect of topical tacrolimus may have triggered bacterial vaginosis in the context of LS being treated with tacrolimus ointment in a 10-year-old girl.(Feito-Rodríguez 2013) 20 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. Lichenoid tissue reactions suggestive of early LS seem to require no adjuvant treatment.(Ebert 2008)

Bohm M, Frieling U, Luger TA, Bonsmann G. Successful treatment of anogenital lichen sclerosus with topical tacrolimus. Arch Dermatol 2003;139:922-4.
Ebert AK, Rosch WH, Vogt T. Safety and tolerability of adjuvant topical tacrolimus treatment in boys with lichen sclerosus: a prospective phase 2 study. European Urology 2008;54:932-7.
Ebert AK, Vogt T, Rosch WH. [Topical therapy of balanitisxeroticaobliterans in childhood. Long-term clinical results and an overview] Urologe 2007;46:1682-6.
Feito-Rodríguez M, Noguera L, Casas-Rivero J, García-Rodríguez J, de Lucas-Laguna R. Bacterial Vaginosis in the Context of Lichen Sclerosus in a Prepubertal Girl. Pediatr Dermatol 2013.
Li Y, Xiao Y, Wang H, Li H, Luo X. Low-concentration topical tacrolimus for the treatment of anogenital lichen sclerosus in childhood: maintenance treatment to reduce recurrence. J Pediatr Adolesc Gynecol 2013;26:239-42.
Matsumoto Y, Yamamoto T, Isobe T, et al. Successful treatment of vulvar lichen sclerosus in a child with low-concentration topical tacrolimus ointment. J Dermatol 2007;34:114-6.

Topical tacrolimus 0.03% ointment appears to be an effective and safe treatment for children (probably mainly applicable in girls) with anogenital LS and a safe maintenance treatment (twice a

week) possibly reducing recurrences. However, as cure is aimed for in boys any treatment that is not curative should be avoided.
Evidence level: 3
Recommendation grade: D

Pimecrolimus

Performing an systematic review Chi et al. found one RCT comparing the efficacy and safety of pimecrolimus(1% cream) and clobetasol propionate (0.05% cream) in the treatment of vulval LS in adults.(Chi 2011; Goldstein 2011) This double-blind, randomized trial of 38 women with biopsy-proven vulval LS had a 12-week treatment period. Both groups showed improvement in pruritus and burning/pain, there was no statistically significant difference (P = 0.32 and 0.93, respectively). Clobetasol was found to be superior in improving inflammation when compared with pimecrolimus (P = 0.015). There were no significant differences in reported adverse drug reactions between groups. Both clobetasol and pimecrolimus appear efficacious and well tolerated for the treatment of vulval LS.

The relief of symptoms in LS by pimecrolimus is also supported by several case series.(Nissi 2007 & 2009; Oskay) 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. There were no systemic adverse reactions, although mild local skin reactions; burning and itching lasting for 3– 14 days were reported in 50% of patients. Blood concentrations of pimecrolimus were checked in 10/26 patients (39%) and were undetectable in all cases.(Nissi 2007) 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.(Nissi et al. 2009)

Women enrolled in a double-blind trial 12-week trial comparing clobetasol vs. pimecrolimus for the treatment of LS were administered the Female Sexual Distress Scale (FSDS) upon enrollment and at the end of the trial. A total of 31 out of 36 enrolled 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).(Burrows 2011)

Burrows LJ, Creasey A, Goldstein AT. The treatment of vulvar lichen sclerosus and female sexual dysfunction. J Sex Med 2011;8:219-22.

Chi CC, Kirtschig G, Baldo M, Brackenbury F, Lewis F, Wojnarowska F. Topical interventions for genital lichen sclerosus. Cochrane Database Syst Rev. 2011 Dec 7;(12)

Goldstein AT, Creasey A, Pfau R, Phillips D, Burrows LJ. A double-blind, randomized controlled trial of clobetasol versus pimecrolimus in patients with vulvar lichen sclerosus. J Am AcadDermatol 2011;64:99-104.

Goldstein AT, Marinoff SC, Christopher K. Pimecrolimus for the treatment of vulvar lichen sclerosus: a report of 4 cases. J Reprod Med 2004;49:778– 780.

Nissi R, Eriksen H, Risteli J, Niemimaa M. Pimecrolimus cream 1% in the treatment of lichen sclerosus. GynecolObstet Invest 2007;63:151– 154.

Nissi R, Kotila V, Knuuti E, Väre PO, Kauppila S. Altered p53 and Bcl- 2 expression in keratinocytes of vulvar lichen sclerosus during pimecrolimus treatment. Br J Dermatol 2009;161:948–970.

Nissi R. P53 expression is down-regulated in lichen sclerosus during pimecrolimus (Elidel) treatment. Maturitas 2009;63:112-3.

Oskay T, Sezer HK, Genç C, Kutluay L. Pimecrolimus 1% cream in the treatment of vulvar lichen sclerosus in postmenopausal women. Int J Dermatol 2007;46:527– 32.

Pimecrolimus and clobetasol propionate are both effective in relieving pruritus and burning/pain in LS. However, pimecrolimus was less effective than clobetasol propionate in relation to the 'investigator-rated global degree of improvement' and therefore clopbetasol propionate should remain first-line therapy for LS. Despite adequate treatment, women with LS continue to have significant sexual dysfunction as assessed by the FSDS.

Evidence level: 1+
Recommendation grade: B

Topical Pimecrolimus in Children

There are few reports of the treatment of LS with pimecrolimus in children.

Boms et al. report on the efficacy of twice-daily application of pimecrolimus 1% cream in four pre-pubertal girls (range of age 4 to 9 years) who suffered from anogenital lichen sclerosus. After three to four-month treatment, all patients had almost complete clinical remission including relief from itch, pain and inflammation. Only minor improvement was observed of the white sclerotic lesions. No significant side effects were observed.(Boms)

Goldstein et al. presented a 10-year-old girl with LS initially treated with clobetasol propionate. Remission was achieved, but 3 months later she had a recurrence. She was then successfully treated with pimecrolimus. She has had no recurrence of active LS and less burning with pimecrolimus than with clobetasol propionate. As the recurrence rate of active LS in prepubertal girls treated with topical corticosteroids is high, and the majority of prepubertal girls with LS continue to have disease after menarche, a treatment regimen that does not rely only on corticosteroids may be beneficial.(Goldstein 2004)

Goldstein AT, Marinoff SC, Christopher K. Pimecrolimus for the treatment of vulvar lichen sclerosus in a premenarchal girl. J PediatrAdolescGynecol 2004;17:35–7.

Boms S, Gambichler T, Freitag M, Altmeyer P, Kreuter A. Pimecrolimus 1% cream for anogenital lichen sclerosus in childhood. BMC Dermatol 2004;4:14.

Fistarol SK, Itin PH. Anti-inflammatory treatment. Curr Probl Dermatol 2011;40:58–70.

Treatment of vulval LS in children / girls with pimecrolimus was effective in few studies; it may be an alternative to topical steroids.
Evidence level: 3
Recommendation grade: D

Summary

Topical calcineurin inhibitors may be an effective alternative to strong topical steroids in the treatment of genital LS, in particular in children (girls). They seem to induce less dermal atrophy; long-term safety aspects need further study.

Retinoids

Topical

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 five days per week for one year. They observed in 76% cessation of itch, 19% improved. 75% had 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, 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.(Virgili 1995) A 84-year-old women suffering from chronic HCV-hepatitis was treated with topical 0.01% tretinoin twice daily for the first month followed by 0.025%. Two month later the pruritus and clinical appearance had improved; there was only slight burning when tretinoin was applied.(Filosa 1997) 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 to 2 months of daily retinoid application. Maintenance treatment followed for 2-4 months once or twice weekly. Follow-up off treatment 4 to 9 months later showed no recurrence. Side-effects were manageable except in one patient who stopped treatment. Serum retinol level in patients was not increased.(Markowska 1992)

An interesting observation is described by Kaya et al. CD44-targeted deficiency in mouse epidermis results in LS-like histological picture.(Kaya 1997) 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 (HA) 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 HA accumulation is a conspicuous feature.(Kaya 2000) It was hypothesized that restoring epidermal CD44 expression might be a therapeutic target in LS. The topical application of retinoids (RA) dramatically increases epidermal CD44 expression at both the protein and mRNA levels in murine and human skin.(Kaya 2005) Retinaldehyde 0.05% , a precursor of precursor of RA, 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 one 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 HA disappeared. (Kaya&Saurat 2005) A double-blind parallel trial in 20 adult patients with biopsy-proven vuval LS comparing mometasone furoate plus RAL with mometasone furoate plus placebo for 6 months did not allow exploration of the effect of RAL monotherapy and lacked potency to demonstrate strong synergy with mometasone furoate.(Harms) It was suggested that agents with the potential of increasing epidermal CD44 should be tried in LS.

Filosa G, Bugatti L, Ciattaglia G. Vulvar lichen sclerosus associated with HCV-related chronic liver disease successfully treated with topical retinoic acid. Chron Derm 1997;7:65-70.

Harms M, Masgrau-Peya E, Lübbe J, et al. Treatment of vulval lichen sclerosus with topical mometasone furoate and retinaldehyde. A double blind study. Abstracts of the 9th Congress of the European Academy of Dermatology and Venereology. J Eur Acad Dermatol Venereol 2000;14 (Suppl. 1):225–6.

Kaya G and Saurat JH. Restored epidermal CD44 expression in lichen sclerosus et atrophicus and clinical improvement with topical application of retinaldehyde. Br J Dermatol 2005;152:570-2.

Kaya G, Grand D, Hotz R, et al. Upregulation of CD44 and hyaluronate synthases by topical retinoids in mouse skin. J Invest Dermatol 2005;124:284–7.

Kaya G, Rodriguez I, Jorcano JL, et al. Selective suppression of CD44 in keratinocytes of mice bearing an antisense CD44 transgene driven by a tissue-specific promoter disrupts hyaluronate metabolism in the skin and impairs keratinocyte proliferation. Genes Dev 1997;11:996–1007.

Kaya G, Augsburger E, Stamenkovic I, Saurat JH. Decrease in epidermal CD44 expression as a potential mechanism for abnormal hyaluronate accumulation in superficial dermis in lichen sclerosus et atrophicus. J Invest Dermatol 2000; 115:1054–8.

Markowska J, Wiese E. Dystrophy of the vulva locally treated with 13-cis retinoic acid. Neoplasma 1992;39:133-5.

Virgili A, Corazza M, Bianchi A, Mollica G, Califano A. Open study of topical 0.025% tretinoin in the treatment of vulvar lichen sclerosus. One year of therapy. J Reprod Med 1995;40:614-8.

Treatment of vulval LS with topical retinoids is thought to have a beneficial effect, but this has not been shown in good studies.
Evidence level: 3
Recommendation grade: D

Summary

Treatment of vulval LS with topical retinoids is thought to have a beneficial effect, they may be tried if topical steroids fail and may be considered for maintenance treatment.

Vitamine E

A randomized trial of topical vitamin E cream compared to emollient following an initial treatment with topical corticosteroid showed similar relapse rate over a one year period, thus vitamin E does not appear to have any advantage over an emollient.

Virgili A, Minghetti S, Borghi A, Corazza M. Long-term maintenance therapy for vulvar lichen sclerosus: the results of a randomized study comparing topical vitamin E with an emollient. Eur J Dermatol 2013;23:189-94.

The treatment of vulval LS with topical Vitamin E has no benefical effect over emollients.
Evidence level: 2+
Recommendation grade: D

Human fibroblast lysate cream

A small double blind placebo controlled industry sponsored trial of topical human fibroblast lysate cream did not show any significant benefit compared to placebo.

Goldstein A, Goldfinger C, Dreher F, et al. Safety and efficacy of human fibroblast lysate cream for vulvar lichen sclerosus. J Am Acad Dermatol 2013;1 AB62 (abstract)

This treatment cannot be recommended for LS

Topical TRPM8 agonist (icilin)

There is is a single case report of the use of topical icilin in LS. Icilin is a TRPM8 receptor antagonist similar to menthol but with a higher affinity to the TRPM8 receptor. Itching was helped but the effect on LS is unknown.

Han JH, Choi H-K, Kim SJ. Topical TRPM8 agonist (icilin) relieved vulva pruritus originating from lichen sclerosus et atrophicus. Acta Dermato Venereol 2012;92:561-2.

Topical TRPM8 agonist reduced pruritus in LS in one case.
Evidence level: 3
Recommendation grade: D

Intralesional adalimumab

There is one case report demonstrating a good response to intralesional adalimumab in a male patient with genital LS.

Lowenstein EB and Zeichner JA. Intralesional adalimumab for the treatment of refractory balanitis xerotica obliterans. JAMA Dermatol 2013;149:23-4.

Intralesional adalimumab may be tried if other treatments fail.
Evidence level: 3
Recommendation grade: D

Topical calcipotriol / calcitriol

One case report of extragenital lichen sclerosus was treated with twice daily 0.005% calcipotriol for 12 weeks under occlusion with good effect.

Kreuter A, Gambichler T, Sauermann K, et al. Extragenital lichen sclerosus successfully treated with topical calcipotriol: evaluation by in vivo confocal laser scanning microscopy. Br J Dermatol 2002;146:332-3.

Topical calcipotriol, possibly under occlusion, may be tried in extragenital LS if first line treatments fail.
Evidence level: 3
Recommendation grade: D

Topical oxatomide

Oxatimide has antihistamine and anti-inflammatory properties. A small, double-blind cross over controlled non-randomized trial of oxatimide versus petrolatum ointment showed significant improvement in pruritus but not is clinical appearances of LS.

Origoni M, Ferrari D, Rossi M, et al. Topical oxatomide: an alternative approach for the treatment of vulvar lichen sclerosus. Int J Gynaecol Obstet 1996;55:259-64.

Oxatomide may help with pruritus associated with vulval lichen sclerosus.
Evidence level: 3
Recommendation grade: D

Moisturizer

An open trial of topical steroid followed by maintenance daily treatment (cold cream) 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.(Simonart) A randomized trial of topical vitamin E cream compared to emollient following an initial treatment with topical corticosteroid showed similar relapse rate over a one year period, thus vitamin E does not appear to have any advantage over an emollient.(Virgili 2013)

Virgili A, Minghetti S, Borghi A, Corazza M. Long-term maintenance therapy for vulvar lichen sclerosus: the results of a randomized study comparing topical vitamin E with an emollient. European Journal of Dermatology 2013;23:189-94.
Simonart T, Lahaye M, Simonart J-M. Vulvar lichen sclerosus: effect of maintenance treatment with a moisturizer on the course of the disease. Menopause 2008;15:74-7.

Emollients may give symptom relief after an initial treatment with topical steroids.
Evidence level: 2+ to 3
Recommendation grade: D

Dermasilk

A controlled randomized double blind study showed that patients undergoing treatment for LS have fewer symptoms when wearing silk rather than cotton briefs.

D'Antuono A, Bellavista S, Negosanti F, et al. Dermasilk briefs in vulvar lichen sclerosus: an adjuvant tool. J Low Genit Tract Dis 2011;15:287-91.

Fewer symptoms from LS are experienced wearing silk rather than cotton briefs.
Evidence level: 2+
Recommendation grade: C

Summary of miscellaneous topical treatments

Many topical preparations are tried in the treatment of LS, however, only few are investigated in series. Topical calcipotriol was effective and can be recommended in extragenital LS. Oxatomide and topical TRPM8 agonist may help reducing pruritus in vulval LS. Moisturizers and silk underwear seem helpful in reducing symptoms in vulval LS. Intralesional adalimumab may be tried if other treatments fail. In single cases or as combined treatment for sometimes unclear diagnoses lavage with potassium permanganate, topical chlorquinaldol, fitostimoline vaginal cream / ovules (damor farmaceutici), topical 1% cidofovir and R 68151, a topical 5- lipoxygenase inhibitor are tried.

UV light

Phototherapy

There are anecdotal reports of the efficacy of psoralen plus UVA (PUVA) and narrow-band UVB for the treatment of extragenital LS.(von Kobyletzki; Colbert; Kreuter 2007) In 2002, the only prospective study on UVA1 (340-400 nm) for extragenital LS in 10 patients reported of an improvement of LS.(Kreuter 2002) The beneficial effect was also confirmed in retrospective case series.(Rombold, Jacobe)

A pilot study on topical PUVA therapy in 12 patients with anogenital lesions of several inflammatory skin diseases included patients with vulval LS.(Reichrath) Clinical improvement (reduction in size of lesions of erythema, and/or of pruritus) was achieved in most patients after 10-20 treatments. An open pilot study of 7 women with severe vulval LS using UVA1 irradiation 3-5 times a week (total exposures 15-65, 192-2212J/cm^2) and emollients reported moderate improvement (including softening of scar tissue, not further specified) in 4, 1 with minimal improvement and 1 with no detectable improvement. Additional UVA1 treatment to extragenital lesions in 2 patients resulted in greater improvement than that seen in genital lesions. Treatment was well tolerated.(Beattie) A randomized clinical trial comparing UVA1 versus 0.05% clobetasol ointment in 30 patients with vulval LS showed a significant improvement of LS in both groups. Both therapies resulted in a significant decrease in mean total clinicians' score (51.4% for clobetasol propionate ointment (P= 0.0003) and 35.6% for UVA1 phototherapy (P=0.0055)); there was no significant difference between treatments (P>0.05).

The Skindex-29 (P=0.0087) and visual analogue scale scores for pruritus (P=0.0047) and burning/pain (P=0.0013) decreased significantly after clobetasol treatment; after UVA1 phototherapy, the visual analogue scale for burning/pain (P=0.0125) was significantly reduced, there was no significant reduction in pruritus (P=0.1572) and in the Skindex-29 score (P=1.000). A significant reduction of the corium thickness and a significant increase in dermal density in 20 MHz ultrasound scanning as well as significant histopathological reduction of the inflammatory infiltrate was only observed after clobetasol treatment, but not after UVA1 phototherapy. The authors conclude that UVA1 was

inferior to topical corticosteroids with respect to practicability, relief of itch, and improvement of quality of life.(Terras)

5 patients with anogenital LS (3 men, 2 women) diagnosed clinically in 5 and histologically in 1 were treated once per week for in average 10 sessions with UVB light (mean dose 0,5 J/cm^2). In 4 patients a reduction in size and thickness was observed.(Nistco 2009)

von Kobyletzki G, Freitag M, Hoffmann K, Altmeyer P, Kerscher M. Balneophotochemotherapy with 8-methoxypsoralen in lichen sclerosis et atrophicus. Hautarzt. 1997;48:488-91.

Colbert RL, Chiang MP, Carlin CS, Fleming M. Progressive extragenital lichen sclerosus successfully treated with narrowband UV-B phototherapy. Arch Dermatol. 2007;143:19-20.

Kreuter A, Jansen T, Stücker M, Herde M, Hoffmann K, Altmeyer P, Von Kobyletzki G. Low-dose ultraviolet-A1 phototherapy for lichen sclerosus et atrophicus. Clin Exp Dermatol. 2001;26:30-2.

Kreuter A, Gambichler T, Avermaete A, Happe M, Bacharach-Buhles M, Hoffmann K, Jansen T, Altmeyer P, von Kobyletzki G. Low-dose ultraviolet A1 phototherapy for extragenital lichen sclerosus: results of a preliminary study. J Am Acad Dermatol. 2002;46:251-5.

Kreuter A, Gambichler T. Narrowband UV-B phototherapy for extragenital lichen sclerosus. Arch Dermatol 2007;143:1213.

Rombold S, Lobisch K, Katzer K, Grazziotin TC, Ring J, Eberlein B. Efficacy of UVA1 phototherapy in 230 patients with various skin diseases. Photodermatol Photoimmunol Photomed. 2008;24:19-23.

Jacobe HT, Cayce R, Nguyen J. Br J Dermatol. UVA1 phototherapy is effective in darker skin: a review of 101 patients of Fitzpatrick skin types I-V. 2008;159:691-6.

Reichrath J, Reinhold U, Tilgen W. Treatment of genito-anal lesions in inflammatory skin diseases with PUVA cream photochemotherapy: an open pilot study in 12 patients. Dermatology. 2002;205:245-8.

Beattie PE, Dawe RS, Ferguson J, Ibbotson SH. UVA1 phototherapy for genital lichen sclerosus. Clin Exp Dermatol. 2006;31:343-7.

Terras S, Gambichler T, Moritz RKC, Stücker M, Kreuter A. Ultraviolet-A1 Phototherapy versus Clobetasol Propionate, 0.05%, in the Treatment of Vulvar Lichen Sclerosus – A Randomized Clinical Trial. JAMA Dermatol 2014; April 02, [Epub ahead of print].

Nistico SP, Saraceno R, Schipani C, Costanzo A, Chimenti S. Different applications of monochromatic excimer light in skin diseases. Photomed Laser Surg 2009;27:647-54.

Phototherapy is effective in some LS patients. Among different UV regimens, the best data is available for UVA1. UVA1 phototherapy is a potential first-line treatment option for extragenital LS. In vulval LS, UVA1 may be considered if topical corticosteroids have failed. However, the well documented development of carcinomas after PUVA and UVB gives cause of concern, in particular at the genital site.

Evidence level: 1+

Recommendation grade: B

Photodynamic therapy

ALA

585-nm Pulsed Dye

Several case reports and small case series evaluated PDT as treatment for recalcitrant vulval LS (Hillemanns, Alexiades-Armenakas, Romero, Sotiriou, Vano-Galvan, Zawislak, Osiecka) and extragenital LS.(Passeron) Randomized controlled studies on PDT in vulval LS are lacking. Twelve women underwent 1–3 cycles of PDT with an argon ion-pumped dye laser (630 nm) at 80 J/cm^2 and a irradiance of 40–70 mW/cm^2 for up to 40 min. Prior to irradiation, the area was occluded with 20% 5-ALA for 4–5 h. Ten of the 12 women showed significant improvement in pruritus that lasted from 3 to 9 months. The procedure was fairly well tolerated although 25% of the patients required opioid analgesia. Histological evaluation was not conclusive.(Hillemanns 1999)

One of 2 patients with severe recalcitrant LS improved after 2 monthly treatments of 20% ALA-PDT with 2 hour-occlusion followed by red light (633 nm) at 30 J/cm2 and 80 mW/cm^2. Vulval lesions healed well and symptoms decreased.(Romero 2007)

Symptomatic improvement after one cycle with 20% ALA for 3 hours followed by red light (570–670 nm, 40 J/cm^2, 80 mW/cm^2) but only minimal change in clinical appearance and no resolution on histological evaluation is reported in 5 patients.(Sotiriou 2008)

28 women were treated with 6 courses of PDT every other week. Pruritus improved in 89% of patients and 35% had complete clearance of LS confirmed by histology.(Olejek 2009)
Skrzypulec et al. focused on sexual function and depressive symptoms after PDT treatment in 37 patients. The study revealed that PDT for LS has no positive effect on sexual functioning but may decrease the severity of depressive symptoms in postmenopausal women However, patients should be informed about the possible lubrication disorders following the treatment.(Skrzypulec) Olejek et al. report a positive effect of PDT in 100 patients; immunhistochemical analyses revealed additional positive effects on microvessel density.(Olejek 2010)

Hillemanns P, Untch M, Prove F, Baumgartner R, Hillemanns M, Korell M. Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid. Obstet Gynecol 1999;93:71–4.
Alexiades-Armenakas M. Laser-mediated photodynamic therapy of lichen sclerosus . JDrugs Dermatol 2004;3(6 Suppl):25-7.
Romero A, Hernández-Núñez A, Córdoba-Guijarro S, Arias-Palomo D, Borbujo-Martínez J. Treatment of recalcitrant erosive vulvar lichen sclerosus with photodynamic therapy. J Am Acad Dermatol 2007;57(2 Suppl):S46–7.
Sotiriou E, Apalla Z, Patsatsi A, Panagiotidou D. Recalcitrant vulvar lichen sclerosis treated with aminolevulinic acid-photodynamic therapy: a report of five cases. J Eur Acad Dermatol Venereol 2008;22:1398–9.
Vano-Galvan S, Fernandez-Guarino M, Beà-Ardebol S, Perez B, Harto A, Jaen P. Successful treatment of erosive vulvar lichen sclerosus with methylaminolaevulinic acid and laser-mediated photodynamic therapy. J Eur Acad Dermatol Venereol 2009;23:71-2.
Sotiriou E, Panagiotidou D, Ioannidis D. An open trial of 5-aminolevulinic acid photodynamic therapy for vulvar lichen sclerosus. Eur J Obstet Gynecol Reprod Biol 2008;141:187-8.
Zawislak AA, McCluggage WG, Donnelly RF, Maxwell P, Price JH, Dobbs SP, McClelland HR, Woolfson AD, Mccarron PA. Response of vulval lichen sclerosus and squamous hyperplasia to photodynamic treatment using sustained topical delivery of aminolevulinic acid from a novel bioadhesive patch system. Photodermatol Photoimmunol Photomed 2009;25:111-3.
Osiecka BJ, Nockowski P, Jurczyszyn K, Ziólkowski P. Photodynamic therapy of vulvar lichen sclerosus et atrophicus in a woman with hypothyreosis--case report. Photodiagnosis Photodyn Ther 2012;9:186-8.
Passeron T, Lacour JP, Ortonne JP. Comparative treatment of extragenital lichen sclerosus with methylaminolevulinic Acid pulsed dye laser-mediated photodynamic therapy or pulsed dye laser alone. Dermatol Surg 2009;35:878-80.
Olejek A, Kozak-Darmas I, Kellas-Sleczka S, Steplewska K, Biniszkiewicz T, Birkner B, Jarek A, Nowak L, Stencel-Gabriel K, Sieron A. Effectiveness of photodynamic therapy in the treatment of lichen sclerosus: cell changes in immunohistochemistry. Neuro Endocrinol Lett 2009;30:547-51.
Skrzypulec V, Olejek A, Drosdzol A, Nowosielski K, Kozak-Darmas I, Wloch S. Sexual functions and depressive symptoms after photodynamic therapy for vulvar lichen sclerosus in postmenopausal women from the Upper Silesian Region of Poland. J Sex Med 2009;6:3395-400.
Olejek A, Steplewska K, Gabriel A, Kozak-Darmas I, Jarek A, Kellas-Sleczka S, Bydliński F, Sieroń-Stołtny K, Horak S, Chełmicki A, Sieroń A. Efficacy of photodynamic therapy in vulvar lichen sclerosus treatment based on immunohistochemical analysis of CD34, CD44, myelin basic protein, and Ki67 antibodies. Int J Gynecol Cancer 2010;20:879-87.

Although potentially effective in relieving symptoms associated with LS, topical PDT does not appear to be associated with an improvement in clinical nor histological response in the limited number of cases studied. PDT may be considered in vulval LS if standard therapy has failed; however, the treatment is painful and time consuming.
Evidence level: 3
Recommendation grade: D

Systemic treatment

Glucocorticosteroids

There is a single retrospective study of the use of pulsed steroid and methotrexate which showed an improvement after in average 3 months´ treatment in extra-genital (partly genital) LS. Patients received an oral dose of methotrexate, 15 mg/wk with high-dose intravenous methylprednisolone

sodium succinate, given as a 1000-mg single dose for 3 consecutive days monthly. Adjustments of the methotrexate dosage were allowed. Treatment was administered to all patients for at least 6 months, improvement of LS was seen in all.

Kreuter A, Tigges C, Gaifullina R, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized extragenital lichen sclerosus. Arch Dermatol 2009;145:1303–8.

Pulsed corticosteroids possibly combined with low dose methotrexate may be an option in generalized treatment resistant LS.
Evidence level: 3
Recommendation grade: D

Oral Retinoids

There are several case series as well as a RCT 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 6 of 8 patients with treatment resistant vulval LS on oral etretinate (1 mg/kg/day) after 14-18 weeks; 3 of the patients stopped treatment and had no flare. Two patients stopped treatment after 10 and 12 weeks because offside effects and no improvement.(Mørk) Romppanen et al. treated 19 women with vulval LS with oral etretinate for 3 months (initial dose 0.54 mg/kg/day, maintenance dose 0.26 mg/kg/day).(Romppanen 1986) A 93% decrease in severity among the group with "severe vulval dystrophy". Two small double-blind, placebo-controlled studies for the treatment of genital LS with acitretin are described.(Bousema; Ioannides) Bousema et al. used in a multi-center trial of 78 patients with vulval LS 20 to 30 mg/day of acitretin for a total of 16 weeks. Of the 78 patients 25 did not meet the inclusion criteria, 7 stopped treatment early because of side effects, 2 on placebo did not have the desired effect, 2 withdrew and one was lost to follow-up. Of the 46 individuals included in the final efficacy analysis, all 22 (100%) patients in the treatment group had significantly less pruritus compared to the placebo group (19/24; 79%) ($p<0.05$); the burning sensation improved in 18/18 (100%) in treatment group compared to 17/19 (85%) in placebo group (no significant difference). A significantly higher number of responders with regard to symptoms (atrophy (86%vs54%), hyperkeratosis (76%vs27%), and secondary features such as erosions, ulcers, edema, or lichenification (57%vs39%) and on the extent of the lesions (36%vs8%)) were observed in the acitretin-treatment group as compared with the placebo-treatment group. Typical retinoid adverse reactions were observed in all patients receiving the active drug (this trial had a low number of patients, the method of randomization is not stated, intention to treat analysis is not preformed). Ioannides et al. performed a RCT in 51 male LS patients treated with either acitretin (n=34) (35 mg) or placebo (n=17) for 20 consecutive weeks. Complete response was achieved by 36% (12 of 33; 1 withdrawn) of the acitretin group vs. 6% (1 of 16; 1 withdrawn) of the controls, while 36% (12 of 33) vs. 13% (2 of 16) achieved partial resolution, respectively. After 36 weeks follow-up 42% of the responders in the treatment group were still in remission the other 58% had worsening of the disease. The mean TCS-score (disease severity score) was in the acitretin group significant lower than in the control group (4,55 compared to 9,31 $p < 0,005$). The quality of life, as determined by the DLQI-method, was after the treatment significantly better than before the treatment (6,76 compared to 12,27 $p < 0,0005$). Based on these results the authors concluded that acitretin is effective in longstanding male LS.

Virgili A, Corazza M, Bianchi A, Mollica G, Califano A. Open study of topical 0.025% tretinoin in the treatment of vulvar lichen sclerosus. One year of therapy. J Reprod Med 1995;40:614-8.

Mørk NJ, Jensen P, Hoel PS. Vulval lichen sclerosus et atrophicus treated with etretinate (Tigason). Acta Derm Venereol 1986;66:363-5.

Romppanen U, Tuimala R, Ellmén J, Lauslahti K. Oral treatment of vulvar dystrophy with an aromatic retinoid, etretinate. Geburtshilfe Frauenheilkd 1986;46:242-7.

Romppanen U, Tuimala R, Ellmen J, Lauslahti K. Treatment of dystrophic changes of the vulva with etretinate or placebo. Curr Ther Res 1987;42:211-8.

Bousema MT, Romppanen U, Geiger JM, Baudin M, Vähä-Eskeli K, Vartiainen J, Vuopala S. Acitretin in the treatment of severe lichen sclerosus et atrophicus of the vulva: a double-blind, placebo-controlled study. J Am Acad Dermatol 1994;30:225-31

Ioannides D, Lazaridou E, Apalla Z, Sotiriou E, Gregoriou S, Rigopoulos D. Acitretin for severe lichen sclerosus of male genitalia: a randomized, placebo controlled study. J Urol 2010;183:1395-9.
Ormerod AD, Campalani E, Goodfield MJD. British Association of Dermatologists guidelines on the efficacy and use of acitretin in dermatology. Br J Dermatol 2010;162:952-963.

There is some data from two small RCTs of not very high quality showing the efficacy of systemic retinoids in the treatment of genital LS. Retinoids may be considered if standard therapy for LS has failed.
Evidence level: 1+
Recommendation grade: B

Miscellaneous oral

Oral Ciclosporin

Five patients with refractory vulvar LS were treated with oral cyclosporine (3-4 mg/kg/d) for 3 months. At the end of the treatment, the mean total symptom score regressed significantly (improvement from 8.6 to 0.8) and clinical findings such as erythema and erosion showed marked improvement one month into treatment. There was sustained improvement even after cessation of treatment. Mild adverse effects were seen in 3 patients (nausea, hypertrichosis, mucositis). Moderate dose of oral cyclosporine could be an effective alternative in the treatment of refractory vulvar LS.(Bulbul 2007)

Bulbul BE, Turan H, Tunali S, et al. Open-label trial of cyclosporine for vulvar lichen sclerosus. J Am Acad Dermatol 2007;57:276-8.

Treatment with oral cyclosporine may be considered in refractory genital LS. Studies in adult men or children were not available.
Evidence level: 3
Recommendation grade: D

Methotrexate

Methotrexate 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.

7 patients with generalized LS (5 genital plus skin; 2 only skin) were treated with (PCMT) high-dose intra-venous methylprednisolone sodium succinate, given as a 1000-mg single dose for 3 consecutive days monthly plus methotrexate 15mg/week 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 during PCMT (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.(Kreuter 2009)

Generalized LS involving the skin and anogenital site was successfully treated with systemic methotrexate 10mg/week for 8 months; at 6 months follow-up off treatment the patient was still in remission. Improvement was noticed by 3 weeks and excellent response after 5 months. The vulval lesions had responded to topical clobetasol but not the cutaneous lesions. (Nayeemuddin 2008)

Kreuter A, Tigges C, Gaifullina R, et al. Pulsed high-dose corticosteroids combined with low-dose methotrexate treatment in patients with refractory generalized extragenital lichen sclerosus. Arch Dermatol 2009;145:1303-8.
Nayeemuddin F and Yates VM. Lichen sclerosus et atrophicus responding to methotrexate. Clin Exp Dermatol 2008;33:651-2.

Methotrexate between 10 and 15 mg/week for 6 months possibly combined with systemic steroids is reported to improve treatment resistant generalized LS.
Evidence level: 3
Recommendation grade: D

Hdroxycarbamide (Hydroxyurea)

Hydroxycarbamide is an antineoplastic drug used in myeloproliferative disorders. It inhibits T lymphocyte proliferation and gamma interferon production and has antiretroviral properties in diseases such as AIDS.

A 67-year-old woman with vulval LS (10-year history) was diagnosed with polycythaemia rubra vera following investigations for malaise. She was started on hydroxycarbamide (hydroxyurea) 1 g daily. Within a month she noticed that her vulval soreness and pruritus had improved and was asymptomatic 6 months later.(Tomson 2007)

Tomson N and Sterling JC. Hydroxycarbamide: a treatment for lichen sclerosus? Br J Dermatol 2007;157:622.

Treatment with hydroxycarbamide (hydroxyurea) 1 g daily was effective after 1 month in the 1 case.
Evidence level: 3
Recommendation grade: D

Cycloferon

Cycloferon is a low molecular weight interferon inducing substance. It exerts antiviral, immunomodulating and anti-inflammatory effects. The drug differs from other interferon inducing substances due to low toxicity and absence of mutagenic, teratogenic, embryotoxic and cancerogenous effects.

A prospective randomized study involved 60 patients with chronic dystrophic diseases of the vulva (45-65 years). Cycloferon i.m. (dose?) on days 1, 2, 4, 6, 8, 10, 12, 16, 20 and 23 was applied in 30 patients; treatment of control group unknown. Cycloferon was reported to induce rapid remission, improvement of QoL and psychosocial function.(Sharapova 2012)

Sharapova LE, Shul'diakov AA, and Liapina EP. [Immunotropic agents in therapy of chronic degenerative diseases of the vulva]. [Russian] Antibiotiki i Khimioterapiia 2012;57(3-4):25-8.

Cycloferon has been tried in LS but detailed information is not available. It cannot be recommended for the treatment of LS.
Evidence level: 3 (there is no information on the control group)
Recommendation grade: D

Fumarate / Dimethylfumarate (DMF)

Fumarate is used in the treatment of plaque psoriasis and is also registered for the treatment of multiple sclerosis. It is reported to induce a shift from a predominantly T-helper-1 type profile in psoriasis to a Th-2 pattern by a direct stimulation of Th-2 cytokine response. DMF induces apoptosis of activated T-cells, interferes with the glutathione metabolism, inhibits the transcription and protein expression of inflammatory cytokines and affects adhesion molecule expression implicated in leukocyte extravasation. It has successfully been used for lichen planus, granuloma annulare, pityriasis rubra pilaris and chronic discoid lupus erythematosus.(Klein 2012) Its use in LS is not reported in the literature, however, there are occasional unpublished observations of the successful use of fumarates in LS.

Klein A, Coras B, Landthaler M, Babilas P. Off-label use of fumarate therapy for granulomatous and inflammatory skin diseases other than psoriasis vulgaris: a retrospective study. J Eur Acad Dermatol Venereol. 2012;26:1400-6.

Treatment with fumarate may be interesting for further evaluation.
Evidence level: 3/4
Recommendation grade: D

Hydroxychloroquine

Hydroxychloroquine is an antimalarial drug, also used to reduce inflammation in the treatment of e.g. rheumatoid arthritis and lupus erythematosus.

There are conflicting case reports of the effect of hydroxychloroquine in bullous cutaneous LS.

A 55-year old woman with generalized LS was treated with oral Hydroxychloroquine 200mg daily, and after 3 months her pruritus had resolved and there was a modest improvement in clinical appearance.(Wakelin 1994; Garcia-Doval 1996; Zierz 1960)

Wakelin SH. and James MP. Extensive lichen sclerosus et atrophicus with bullae and ulceration-improvement with hydroxychloroquine. Clin Exp Dermatol 1994;19:332-4.

Garcia-Doval I, Peteiro C, Sánchez-Aguilar D, Toribio J. Extensive bullous lichen sclerosus et atrophicus unresponsive to hydroxychloroquine. Clin Exp Dermatol 1996:21:247.

Zierz P and Kantner M. Histolohcal changes in lichen sclerosus atrofhicans during treatment with

resochin. [German] Cloroquine. Acta Neurovegetativa 1960;21:215-226.

Treatment with hydroxychloroquine cannot be recommended.
Evidence level: 3
Recommendation grade: D

Antibiotics (penicillins, cephalosporins, dirithromycin etc.)

After unsuccessful circumcision for penile LS intramuscular penicillin G benzathine (2.4 million U), oral penicillin V potassium 500 mg 4 times daily, and the interdiction of all local treatment led to dramatic improvement within several weeks, which was sustained with injections of penicillin G benzathine (2.4 million U) at 2-month intervals, and continuation of oral penicillin V potassium. After 1 year, excellent control of LS was achieved in two man.

Cefuroxime axetil 150 mg 3x/day and azithromycin 250 mg/day resulted in variable results in a 41-year-old male with penile LS allergic to penicillin. However, dirithromycin 250 mg, 2 capsules each morning, produced rapid improvement and greatly lessened the pain. Stopping the dirithromycin after 1 month resulted in relapse, so it was resumed and continued for 6 months, with further improvement. Previous topical steroids and surgery were unsuccessful.(Shelley 1999)

15 women and men with steroid resistant genital LS were treated with either penicillin or a cephalosporin (penicillin G benzathine suspension (long-acting) 2.4 million units intramuscular every 2 weeks or penicillin V potassium 500 mg b.i.d., oral or penicillin V potassium 500 mg q.i.d., oral or amoxicillin/clavulanate potassium 250 mg t.i.d., oral or amoxicillin 500 mg b.i.d., oral or cefadroxil monohydrate 500 mg b.i.d., oral or ceftriaxone sodium 1 g intramuscular every 3 weeks). Good (4) to moderate (7) improvement was achieved after several months treatment.(Shelley 2006)

Shelley WB, Shelley ED, Grunenwald MA, et al. Long-term antibiotic therapy for balanitis xerotica obliterans. J Am Acad Dermatol 1999;40:69-72.

Shelley WB, Shelley ED, Amurao CV. Treatment of lichen sclerosus with antibiotics. International Journal of Dermatology 2006;45:1104-6.

Penicillins and cephalosporins (Ceftriaxone 1 g intramuscular every 2 weeks for three doses, and then once a month on a p.r.n. basis or penicillin G benzathine suspension (long acting) 2.4 million units intramuscular every 2 weeks for three doses, and then once a month on a p.r.n. basis) showed some improvement and may be tried in topical steroid resistant genital LS.
Evidence level: 3
Recommendation grade: D

Sulphasalazine

Sulfasalazine, a sulfa drug and derivative of mesalazine, is formed by combining sulfapyridine and salicylate and is used in the treatment of inflammatory bowel disease and rheumatoid arthritis. Because sulfasalazine and its metabolite 5-aminosalicylic acid are poorly absorbed into the bloodstream, it is likely that the other metabolite, sulfapyridine, is responsible for the anti-arthritic effects.

A 75-year old woman with cutaneous LS (on histology, DD morphea) was treated with oral sulfasalazine(salazopyrine) 2 g/day. After one month improvement was noticed, salazopyrine was reduced to 1.5 g/day. Cessation of treatment resulted in itch, restoration of 1 g/day improved symptoms; 10 years later, the subject was still in remission (on treatment); adverse effects were not noted.

Taveira M Selores M, Costa V, Massa A. Generalized morphea and lichen sclerosus et atrophicus successfully treated with sulphasalazine. J Eur Acad Dermatol Venereol 1999;12:283-4.

Sulphasalazine(salazopyrine) 1- 2 g/day may be tried in cutaneous LS.
Evidence level: 3
Recommendation grade: D

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. Various cells in the skin express the vitamin D receptor and convert circulating 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D for local use. This metabolite has been shown to exert potent effects on

cellular differentiation, cellular proliferation, and immune regulation. Calcitriol is the biologically active form of Vit D acting on e.g. fibroblasts and lymphocytes.
One patient with cutaneous generalized LS resistant to different therapeutics was treated with calcitriol in an oral daily dose of 0.5 microgramme. After 6 months of treatment, the skin extensibility increased, and the lesions improved. The improvement persisted after discontinuation of therapy during a follow-up period of one year. The only side effect was hypercalciuria, which resolved with dose reduction. Double blind, placebo-controlled trials are needed to assess the therapeutic value of calcitriol in patients with LS.(Ronger 2003)

Ronger S, Viallard AM, Meunier-Mure F, et al. Oral calcitriol: a new therapeutic agent in cutaneous lichen sclerosus. J Drugs Dermatol 2003;2:23-8.

Oral Vitamin D was effective in cutaneous LS in one patient.
Evidence level: 3
Recommendation grade: D

Vitamin A & E

Vitamin A plays a role in regulating epithelial proliferation and differentiation; there are anti-oxidant effects of Vitamin E.
Eleven patients with vulval LS were given Vitamin A + Vitamin E orally for 12 months without any topical treatment (Vit A 120.000U&VitE 280mg twice daily for 10 days/month for 2 months, then VitA 80000U&VitE 210 twice daily for 10 days/month for 4 months, then VitA 60000U&VitE 140 twice daily for 10 days/month for 6 months). Clinical improvement was seen in 91% after 6 months of treatment (3 no more symptoms, 7 significant improvement, 1 no response). On follow-up 9 patients had no relapse after 1 year off treatment, in 1 pruritus recurred after 6 months. There were no side effects. Histological patterns were unaltered after therapy.(Calista 1994)

Calista D, Cappelli MC, Foglietta F, Gambi A. Vitamins A and E in the treatment of atrophic lichen sclerosus of the vulva. [Italian]. Vitamine a Ed E Nel Trattamento Del Lichen Scleroatrofico Vulvare. Specializzati Oggi - Dermatologia 1994;**3**:12-14.

Oral Vitamin A and E showed some improvement of genital LS in one series
Evidence level: 3
Recommendation grade: D

Potassium para-aminobenzoate

PABA is an intermediate in the bacterial synthesis of folate (Vitamin Bx) and is structurally similar to Sulfonamide drugs. The potassium salt is used as a drug against fibrotic skin disorders.
In five patients with symptomatic cutaneous LS, significant clinical improvement was obtained following the administration of potassium para-aminobenzoate. Improvement was characterized by a marked decrease or absence of symptoms and a flattening of skin lesions. Doses ranged from 4 to 24 g daily, in divided doses after 1 day to 8 weeks; there are few reported side effects.(Penneys 1984)
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 two 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.(Buxton 1990)

Penneys NS. Treatment of lichen sclerosus with potassium para-aminobenzoate. J Am Acad Dermatol 1984;10:1039-42.
Buxton PK and Priestley GC. Para-aminobenzoate in lichen sclerosus et atrophicus. Journal of Dermatological Treatment 1990;1:255-6.

Potassium para-aminobenzoate from 4 to 24 g daily, in divided doses is reported to improve cutaneous LS after 1 day to 8 weeks. A RCT comparing Potaba 12g/d versus placebo showed no significant difference. This medication cannot be recommended for the treatment of LS.
Evidence level: 1+
Recommendation grade: B

Summary

Oral Cyclosporine, Methotrexate, Hdroxycarbamide, Cycloferon, Ceftriaxone, Penicillin G, Sulfasalazine, Vitamin A combined with Vitamin E or Vitamin D may be tried in treatment resistant

LS. The level of evidence and grade of recommendation are very low and not always are the drugs tried in all forms of LS. Potassium para-aminobenzoate cannot be recommended.

Surgery

Conventional Surgery

Males

"There is no surgical gold standard for the treatment of male genital lichen sclerosus (male genital LS). All recommendations have been based on non-randomized studies and expert opinion".(Stewart 2013)

Boys

Circumcision

There are several studies which point out the curative effect of complete circumcision in boys. In a prospective study 10 cases of boys with LS were clinically controlled 5 years after surgery and showed no signs of recurrence.(Meuli 1994) This observation was confirmed in a much greater prospective series of 471 LS cases. 471 boys were followed up for 12 months postoperatively, then yearly. 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 lesions in two boys only resolved in the second year post-surgery.(Kiss 2005) Suggesting that postoperative anti-inflammatory treatment is not necessary.

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.(Becker 2011)

A recent study showed the successful combination of preputioplasty and intraoperative injection of triamcinolon into the LS lesions in 84 out of 104 cases. 84 of 104 (81%) in the preputioplasty group had a fully retractile foreskin and no macroscopic evidence of BXO. Of 104, 14 (13%) developed recurrent symptoms/BXO requiring circumcision or repeat foreskin preputioplasty.(Wilkinson)

Recurrence after complete circumcision is reported anecdotally in cases of obese boys with buried (concealed) penis.(Depasquale 2000, Gargollo 2005, Becker 2011)

Circumcision with complete removal of the foreskin is curative in most LS cases in boys unless LS is present in hypospadias repair or in obese boys, in these two groups there is a considerable risk of recurrence.
Foreskin-saving preputioplsty combined with steroid injections was successfully performed in the majority of cases in one study; further studies have to confirm this.
Evidence level: 3
Recommendation grade: D

Meatodilatation, Meatotomy, Meatoplasty

The rate of meatal stenosis is reported to be observed in 2%-37% of LS-cases.(Kiss 2005, Gargollo 2005) Meatal stenosis can be part of the initial clinical picture or develop several months after circumcision. Results of surgical interventions are good.

Urethral surgery

Urethral LS tends to occur after surgery for hypospadia. This will lead to more extensive plastic surgery which is reviewed below (men). In a descriptive analysis of 1.176 patients with failed hypospadias repair requiring further surgery 89 (7.6%) had histologically proven LS (Barbagli 2010). Apart from these special circumstances urethral LS in boys has been reported in only 5 cases (2 out of 130 LS-cases: Barbagli 2004; 3 out of 41 LS-cases: Gargollo 2005. Both studies collected data over a period of 10 years. All five underwent one or more procedures (circumcision, cystoscopy)before the development of urethral LS.

Surgery of the meatus should be performed if necessary (stenosis). Follow-up at 6 months after the circumcision carefully investigating the meatus and glans is recommended.(It is not clear from the literature if anti-inflammatory treatment applied after the operation is beneficial)
Urethral surgery in boys is normally not required and limited to special cases (i.e. hypospadia, obesity with buried penis)

Evidence level: 3
Recommendation grade: D

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 removement of the foreskin (circumcision).(Depasquale 2000) 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.(Kulkarni 2009) Long term follow up studies have not been done.

Circumcision in LS with complete removal of the foreskin is claimed to be curative in 90 - 100% if limited to foreskin and glans
Evidence level: 3
Recommendation grade: D

Glans resurfacing

If LS remains active on the surface of the glans after circumcision topical treatment seems to be of limited benefit (Garaffa used only "mild" topical steroids, Depasquale used clobetasol propionate). 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".(Garaffa 2011; Morey 2011)

Glans resurfacing in cases of persistent glanular LS is successful in the majority of patients.
Evidence level: 3
Recommendation grade: D

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%).(Parkash 1984) Some, therefore, prefer meatoplasty (85% satisfactory results reported).(Malone 2004) Long-term results (10 years) are "excellent".(Bhatt 2010; Treiyer 2011) 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).(Kulkarni 2009)

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.(Barbagli 2012)

A generous ventral meatotomy followed by anti-inflammatory topical treatment may help.(Singh 2011) 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 muccosa graft is recommended.(Singh 2011) But both meatotomy and meatoplasty may result in stricture recurrence (20.5% vs 7.5%, p=0.04).(Meeks 2011)

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). Patient 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.(Meeks 2011)
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 epidermization of the urethral mucosa, creating the basis for LS to diffuse into the remaining tract.(Barbagli 2011)

Meatal surgery depends on the extent of the stricture, the needs of the patient and the experience of the surgeon. Dilation is thought to bear the highest risk of recurrence.
Evidence level: 3
Recommendation grade: D

Urethroplasty
Urethroplasty of urethral strictures in LS is regarded as 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.(Venn 1998)
Moreover a oral mucosa graft is regarded as the tissue of choice for urethroplasty of urethral strictures due to LS.(Stewart 2013) Most commonly used are buccal muccosa grafts from one or both cheeks but mucosal grafts from the inner lips and even the tongue seem also to be suitable.(Das 2009) There are still authors advocating bladder mucosa or even colonic mucosa but this means an abdominal incision to harvest the graft.(Martinez-Pineiro 2009)
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 to 9 years follow-up.(Depasquale)
In recent years most data support a more differentiated surgical strategy which consists of one stage dorsal oral mucosa onlay graft urethroplasty (Barbagli 1996) extending the buccal mucosa grafts to the meatus thus creating a dorsal meatoplasty (Dubey 2005) in selected cases.
If the stricture is limited to the penile urethra the procedure can be performed by a circumcoronal incision, degloving 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.(Kulkarni 2000)
Dubey et al. recommend a one-stage dorsal buccal mucosa onlay urethroplasty if preliminary urethroscopy reveales a urethral caliber of more than 6 Fr and the urethral plate is not severely scarred.(Dubey) 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 ratesfollowing this strategy are reported to be 80 - 90% with a mean follow up of 32 to 58 months.(Dubey 2005, Trivedi 2008, Kulkarni 2009)
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.(Wessels 1996)The dorsal onlay graft seems to solve this problem.(Barbagli 2003)
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 is recommended.(Kulkarni, Dubey, Trivedi) During the first stage a perineal urethrostomy is made. The urethra is excised and mucosal graft applied. In the second stage the neourethra is tubularized, connected with the proximal urethra and uerethrostomy is closed 4-6 month 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 preferto 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.(Kulkarni 2009)
The discussion concerning the best treatment of urethral stricture in LS is ongoing. Results of longterm follow-up (10 years) combined with analysis of quality of life of these patients are awaited.(Kulkarni 2009)

The extension of urethral stricture has to be defined. Principally one-stage or two-stage procedures with replacement or onlay augmentation of the diseased urethra are recommended options.
Evidence level: 3
Recommendation grade: D
The use of mucosal grafts instead of non-genital skin is highly recommended with buccal mucosa as the tissue of choice.
Evidence level: 3
Recommendation grade: D
In severe cases or elderly patients a perineal urethrostomy as final solution may be preferable and should be discussed with the patient.
Evidence level: 3
Recommendation grade: D

Summary

Circumcision is curative in most cases of early and intermediate LS in males, restricted to prepuce and glans. An initial curative attempt with ultrapotent topical corticoid treatment should be offered. In early and mild cases cure can be achieved and prepuce preserved, but follow-up has to be secured. Any non-symptom free status of LS after medical treatment should not be accepted because of the high possibility of cure after surgical treatment with a symptom free status.
In more complex cases with urethral involvement reconstructive surgery may be necessary and provides good results if performed by experienced urethral surgeons.

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Barbagli G, Mirri F, Gallucci M, Sansalone S, Romano G, Lazzeri M. Histological evidence of urethral involvement in male patients with genital lichen sclerosus: a preliminary report. J Urol 2011;185:2171-6.

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Depasquale I, Park AJ, Bracka A. The treatment of balanitis xerotica obliterans. BJU Int 2000;86:459-65.

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Garaffa G, Shabbir M, Christopher N, Minhas S, Ralph DJ. The surgical management of lichen sclerosus of the glans penis: our experience and review of the literature. J Sex Med 2011;8:1246-53.
Gargollo PC, Kozakewich HP, Bauer SB, et al. Balanitis xerotica obliterans in boys. J Urol 2005;174:1409-12.
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Kulkarni S, Barbagli G, Kirpekar D, Mirri F, Lazzeri M. Lichen sclerosus of the male genitalia and urethra: surgical options and results in a multicenter international experience with 215 patients. Eur Urol 2009;55:945-54.
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Venn SN, Mundy AR. Urethroplasty for balanitis xerotica obliterans. Br J Urol 1998;81:735-7.

Conventional surgery

Females

Over the last 40 years a few single center cohort studies and various case reports of surgery in females with symptomatic anogenital LS have been published. There are no data from randomized trials available.

Vulvectomy

Neither radical nor skinning vulvectomy is an adequate method to treat LS successfully, since the procedure is mutilating and the recurrence rate is above 50%.(Abramov 1996; Rojavin 2008) Vulvectomy is limited to vulval cancer and precancerous lesions; associated residual LS in these patients contributes to a high recurrence rate of LS.(Regauer 2011)

Even though some authors are positive about the outcome after vulvectomy the long-term outcome and quality of the published studies does not justify vulvectomy in uncomplicated LS, it should be reserved for LS associated with vulval malignancy. Evidence level: 4 Recommendation grade: D

Labial adhesions and introitus stenosis

In women with stenosis of the introitus vaginae and/or labial adhesions, 3 retrospective cohort studies with chart review and invited questionnaire on 124 women report that simple perineotomy and reconstruction achieves improvement in quality of life in approximately 80-90% of women, but long-term data are only available in a few patients.(Rouzier 2002; Gurumurthy 2012; Bradford 2013) In patients with persistent symptoms (dyspareunia) after failure of perineotomy one cohort study reports on satsifactory results by reconstruction of the posterior fourchette by double opposing z-plasty with VY advancement in a small number of patients.(Frappell 2012) However, only a

proportion of patients will have sexual intercourse after any of these procedures and even a smaller proportion will have sex without pain. Perioperative suppression of the inflammatory process by medical treatment was recommended to improve the surgical outcome.(Bradford 2013)

Minor surgical procedures like perineotomy, de-adhesiolysis or Z-plasty can relief symptomatic vulval LS (dyspareunia) in highly selected patients. Surgery should be combined with perioperative anti-inflammatory treatment and the use of dilators and/or early resumption of intercourse after surgery to prevent restenosis.
Evidence level: 3
Recommendation grade: D

Clitoral phimosis and urethral stricture

Fusion of the clitoral hood leading to a buried clitoris is a common problem in LS and will reduce the quality of life in many women. Treatment of clitoral phimosis is difficult as surgery at the site may lead to loss of sensitivity and for others releasing the hood may cause extreme sensitivity very difficult to cope with. Therefore, early treatment (in women and girls) should aim for preventing clitoral fusion using topical steroids and moisturizers; early preventive treatment around the clitoris, even if not symptomatic, may be recommended.

However, like labial adhesions, symptomatic clitoral phimosis may successfully be treated in selected cases by minor surgery procedures like CO2-Laser division or hydrodissection in combination with reverse V-plasty, as shown by two prospective cohort studies with acceptable follow-up results.(Ostrzenski 2010; Kroft 2012) Urethral stricture is more common in male patients, but also a few women with LS will suffer from an affected distal urethra and urethroplasty with oral mucosal graft seems to be an option even in women.(Bradley 2013) These procedures should only be performed by experienced surgeons.

Abramov Y, Elchalal U, Abramov D, Goldfarb A, Schenker JG. Surgical treatment of vulvar lichen sclerosus: a review. Obstet Gynecol Surv 1996;51:193-9.

Bradford J, Fischer G. Surgical division of labial adhesions in vulvar lichen sclerosus and lichen planus. J Low Genit Tract Dis 2013;17:48-50.

Bradley P, Ordorica R. Alternative oral mucosa grafts. J Urol 2013;1:154.

Frapell JM. Double opposing zplasty with VY advancement. A new operation for failed Fenton's procedure. Int J Gynecol Obstet 2012;119:352.

Gurumurthy M, Morah N, Gioffre G, Cruickshank ME. The surgical management of complications of vulval lichen sclerosus. Eur J Obstet Gynecol Reprod Biol 2012;162:79-82.

Kroft J, Shier A. A novel approach to the surgical management of clitoral phimosis. J Obstet Gynaecol Can 2012;34:465-71.

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Regauer S. Residual anogenital lichen sclerosus after cancer surgery has a high risk for recurrence: a clinicopathological study of 75 women. Gynecol Oncol 2011;123:289-94.

Rojavin Y, Salgado CJ, Hsu PW, Liu J, Aikins JK. The surgical management of vulvar lichen sclerosus refractory to medical management. J Plast Reconstr Aesth Surg 2008;61:848-9.

Rouzier R, Haddad B, Deyrolle C, Pelisse M, Moyal-Barracco M, Paniel BJ. Perineoplasty for the treatment of introital stenosis related to vulvar lichen sclerosus. Am J Obstet Gynecol 2002;186:49-52.

CO2-Laser division or hydrodissection in combination with reverse V-plasty for symptomatic clitoral phimosis and urethroplasty with oral mucosal graft in distal urethral stenosis may be successful in some patients.
Evidence level: 3
Recommendation grade: D

Summary

Beside indications for cancer treatment, surgery for female patients with LS should be preserved for highly selected symptomatic LS in women with clitoral phimosis, introitus stenosis or labial adhesions. Minor surgery is adequate to achieve symptom relief in some patients and might peri-operatively be combined with medical treatment to suppress the inflammatory process. Extended surgery is not suitable to cure the disease. Any reconstructive surgery techniques using alloplastic or

heteroplastic material in female patients should be regarded as experimental and cannot be recommended.

Miscellaneous Surgery

Punch grafts, tangential excision in extragenital bullous LS, dermabrasion and, cryosurgery have all been performed in single cases or small series; none can be recommended as recurrence rates are high.

Malakar S and Dhar S. Punch grafting in lichen sclerosus et atrophicus. Dermatology 1997;195:412.

Klein LE, Cohen SR, Weinstein M. Bullous lichen sclerosus et atrophicus: treatment by tangential excision. J Am Acad Dermatol 1984;10:346-50.

Miller RF. Lichen sclerosus et atrophicus with oral involvement; histopathologic study and dermabrasive treatment. A. M. A. Arch Dermatol 1957;76:43-55.

Kastner U, Altmeyer P. Cryosurgery--the last resort or a surgical alternative in the treatment of lichen sclerosus et atrophicus of the vulva?. [Article in German] J Dtsch Dermatol Ges 2003;1:206-11.

Stücker M, Grape J, Bechara FG, Hoffmann K, Altmeyer P. The outcome after cryosurgery and intralesional steroid injection in vulvar lichen sclerosus corresponds to preoperative histopathological findings. Dermatology 2005;210:218-22.

CO2 Laser

There are a few prospective case series reporting the successful treatment of mainly penile but also vulval LS with CO2 laser.

Patients remained free of LS after two or three sessions with CO2 laser vaporization (40 watts, 3-mm depth, 1-mm spot, in defocus); the vaporization endpoint was to reach the yellowish normal submucosal tissue and normal epithelium laterally.(Aynaud 2010)

Circumferential carbon dioxide laser vaporization successfully treated balanitis xerotica obliterans associated meatal stenosis in 4 male patients; voiding improved after the treatment in all.(Hrebinko 1996)

10 patients (five women and five men) with penile, perineal and extragenital LS were treated with complete remission in 4 men and a recurrence of urethral LS in 1. The cutaneous lesions responded better to treatment than the perineal lesions in women. The mean follow-up time was 32 months (range 3-79 months). The authors concluded that skin lesions respond better than perineal lesions.(Kartamaa 1997)

Seven patients with vulval LS were treated by laser ablation (density of 600-900 W/cm^2) of the affected area (including labia minora & periclitoral area demarcated by hymenal ring and hairline) to a depth of 1.0 to 2.0 mm. The inpatient procedure was performed under general anesthesia; healing was complete 6 weeks postoperatively. 6 of 7 patients were free of recurrent symptoms at follow-up of 12 to 37 or 27 months (discrepancy in abstract vs text), one of those continued to use topical testosterone.(Stuart 1991)

62 consecutive patients (who had various treatments, mainly topical steroids, before laser treatment) were treated with a carbon dioxide laser with an output of 15-20 W and a defocused beam (wavelength of 10,000nm) between 1985 and 1991. The macroscopically altered area of the glans penis was vaporized, if applicable phimosis (in 38) and superficial meatal stenosis were treated at the same session. Healing was achieved after 6-8 weeks. At follow-up after 3 months to 7 years (average 30 months) 76% had no local symptoms; symptomatic were mainly patients who had involvement of the frenulum.2 patients of the group developed penile SCCs. After an average of 14 years 50 patients could be reviewed; 40 (80%) had no symptoms and no visible lesion. Ten patients had minor symptoms but only two required further treatment.(Windahl 2006)

Adverse effects include postoperative pain and vaginal and vulval adenosis.(Sedlacek 1990)

Aynaud O, Plantier R. Genital lichen sclerosus treated by carbon dioxide laser. Eur J Dermatol 2010;20:387-388.

Hrebinko RL. Circumferential laser vaporization for severe meatal stenosis secondary to balanitis xerotica obliterans. Journal of Urology 1996;156:1735-6.

Kartamaa M, Reitamo S. Treatment of lichen sclerosus with carbon dioxide laser vaporization. Br J Dermatol 1997;136:356-9.

Stuart GC, Nation JG, Malliah VS, Robertson DI. Laser therapy of vulvar lichen sclerosus et atrophicus.

Canadian Journal of Surgery 1991;34:469-70.
Sedlacek TV, Riva JM, Magen AB, et al. Vaginal and vulvar adenosis. An unsuspected side effect of CO2 laser vaporization. J Reprod Med 1990;35:95-1001.
Windahl T. Is carbon dioxide laser treatment of lichen sclerosus effective in the long run? Scandinavian Journal of Urology & Nephrology 2006;40:208-11.

CO2 laser treatment is shown to be effective in cutaneous and genital LS; also long-term results in penile LS (between 70 and 80%) were good.
Evidence level: 3-2+
Recommendation grade: D-C

Summary

CO2-laser ablation is shown to be effective in the treatment of LS and may be tried in cutaneous and symptomatic vulval and particularly penile LS including meatal stenosis if standard treatment has failed; involvement of the frenulum seems to be associated with less good outcome.

Focused Ultrasound

There are few case series reporting about the results of focused ultrasound in the treatment of "white" vulval lesions, including LS and vulval squamous hyperplasia. The reports come exclusively from China and are mainly published in Chinese. Focused ultrasound is thought to stimulate cell proliferation, protein synthesis and revascularization, and accelerate tissue reconstruction, improve microcirculation and nutrition of the local tissues. Furthermore, after elimination of local inflammation, the stimulus of nerve endings is thought to be reduced, leading to a reduction of vulval pruritus or visible lesions.

31 patients with vulval LS were treated under local anaesthesia with a water pump system which sends frequencies of 5 to 8 MHz via an applicator of 12 mm in diameter that is in direct contact with the skin. The target are dermal skin structures. The treatment takes 15 to 60 minutes depending on the size of the lesion. 17 patients were "cured" and 12 improved after treatment evaluating pruritus, skin elasticity, colour, and histological changes after max. 2 year follow-up. Side effects were transient local inflammation with blister formation in 5%.(Li 2004)

41 women with vulval LS were treated prospectively with HIFU(Model CZF-2, Chongqing Haifu [HIFU] Technology, Chongqing, China) using a transducer's power range between 3.0 and 4.7Watts and a frequency between 9 and10MHz according to the method described by Li in 2004. At 6 months 13 patients were "cured", 21 had improved, in 7 there was persistent disease and 4 had a recurrence; the same evaluation criteria were applied as described by Li 2004; similar adverse effects were described. In the same study patients with squamous cell hyperplasia were treated also; the outcome and complication rate was favourable in this group compared to the group of patients with LS.(Ruan 2010)

Li C, Bian D, Chen W, et al. Focused ultrasound therapy of vulvar dystrophies: a feasibility study. Obstetrics & Gynecology 2004;104:915-21.
Ruan L, Xie Z, Wang H, et al. High-intensity focused ultrasound treatment for non-neoplastic epithelial disorders of the vulva. International Journal of Gynaecology & Obstetrics 2010;109:167-70.
Zhu JH, Feng LH, Zheng H, et al. [Evaluation of curative effects of focused ultrasound treatment for nonneoplastic epithelial disorders of vulva] Journal of Jilin University (Medicine Edition) 2006;32:714-6.

Focused ultrasound is reported to be beneficial in the treatment of LS. Authors report of 30 to 50% "cure". However, long term results are lacking.
Evidence level: 3
Recommendation grade: D

Summary

Focused ultrasound may be tried if standard treatment has failed.

Stem cells and platelet rich plasma

Lipofilling techniques have been used for other conditions e.g. post radiotherapy and growth factors released by platelets have an important role in inflammation reduction, angiogenesis stimulation, and collagen III synthesis.

Fifteen female patients with histologically diagnosed treatment resistant lichen sclerosus were treated with platelet-rich plasma and adipose tissue.(Casabona 2010) Liposuction was carried out from a donor region and processed lipoaspirate was injected in the damaged area. 5 ml of platelet-rich plasma containing 0.5 ml of calcium chloride for platelet degranulation was injected into the same areas in the intradermal-intramucosal, subdermal, and submucosal compartments. Fifteen days after intervention, symptoms improved, itching and burning disappeared within 1 month. Vulvar skin and mucosa appeared more elastic and soft, with a normal color. Four months after surgery, all patients reported total disappearance of pain and symptoms, and the anatomical features of the vulva were "quite normal". All patients regained sexual activity. Patients with severe fibrosis and atrophy underwent the procedure again 3 months later, with satisfactory and stable results. Follow-up ranged from 6 to 24 months.
The same group described their 5-year experience of 127 LS patients. Clinical applications of adipose derived stem cells and platelet rich plasma are thought to stimulate angiogenesis, fibroblasts and collagen synthesis for tissue reconstruction. 127 patients betwee22 to 74 years received 1 to 4 treatments depending on the degree of the lesions, with 3 months intervals. 318 treatments were performed without complications. Improvement was observed after 1 month, in urethral dislocation, repositioning and normalization of the urinary flow was observed. Follow-up showed stable results.(Casabona 2012)

Casabona F, Robello G, Cogliandro A, et al. Nuova terapia degli esiti di lichen sclerosus della vulva con L'impiego de cellule multipotenti di derivazione adipose e plasma ricco di piastrine: case report. Riv Ital Chir Plast 2008;40:67-70.

Casabona F, Priano V, Vallerino V, et al. New surgical approach to lichen sclerosus of the vulva: the role of adipose-derived mesenchymal cells and platelet-rich plasma in tissue regeneration Plastic & Reconstructive Surgery 2010;126:210-211.

Casabona F, Priano V, Piri C, Vallerino V. New regenerative approach to lichen sclerosus of the vulva with adipose derived stem cells and platelet rich plasma. 5 Years experience. International Journal of Gynecology and Obstetrics 2012;119:307.(abstract only)

Stem cells and platelet rich plasma is used in a case series with promising results by one group. It is not known whether both components of the treatment are necessary. Results are not confirmed by others; there is no data about costs. It is difficult to recommend this potentially promising treatment whilst there are no detailed results published.
Evidence level: 3-4
Recommendation grade: D

Patients' prospective

If you ask a patient what doctors need to do for patients with LS?

- They need to start treatment early.
- Try to keep it under control to avoid scarring and surgery.
- Educate patients on the importance of taking care of the vulva / penis once LS is affecting it.
- Doctors need to start a co-operative or special sub-group, internationally, with the European societies, ISSVD and BSSVD and work together on a good study, over a number of years, if we are to make a better future for our children growing up with LS and for those that will go on to get this problem.
- Time we stopped young women losing clitoral function due to poor knowledge and lack of concern.

Margesson LJ. Practice gaps: Practice gaps "down there": failures in education, physical examination, recognition, diagnosis, therapy, follow-up care, and cancer surveillance in lichen sclerosus. JAMA Dermatol 2013;149:1203.

Existing guidelines / Audits

Edwards S, Handfield-Jones S, Gull S; Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). National guideline on the management of vulval conditions. Int J STD AIDS 2002;13:411-5.

Neill SM, Tatnall FM, Cox NH; British Association of Dermatologists. Guidelines for the management of lichen sclerosus. Br J Dermatol 2002;147:640-9.
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Neill SM, Lewis FM, Tatnall FM, Cox NH; British Association of Dermatologists. British Association of Dermatologists' guidelines for the management of lichen sclerosus 2010. Br J Dermatol 2010;163:672-82.
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Thorstensen KA, Birenbaum DL. Recognition and management of vulvar dermatologic conditions: lichen sclerosus, lichen planus, and lichen simplex chronicus. J Midwifery Womens Health 2012;57:260-75.
Dutch guideline for lichen sclerosus: „Richtlijn lichen sclerosus", NVDV 2012, Netherlands
Ngu WC, Green C. Clinical audit: Long-term follow-up of women with genital lichen sclerosus. BMC Proceedings, 2012. 6.
Pratsou P. Managing lichen sclerosus - How well do we do? HIV Medicine 2010;11:90-91.
Fistarol SK, Itin PH. Diagnosis and treatment of lichen sclerosus: an update. American Journal of Clinical Dermatology 2013;14:27-47.
Pérez-López FR, Ceausu I, Depypere H, et al. EMAS clinical guide: Vulvar lichen sclerosus in peri- and postmenopausal women. Maturitas 2013;74:279-82.
Raj G, Bell HK. A multi-centre audit on genital Lichen sclerosus in the North West of England. J Eur Acad Dermatol Venereol 2013 [Epub ahead of print]
Brodrick B, Belkin ZR, Goldstein AT. Influence of treatments on prognosis for vulvar lichen sclerosus: Facts and controversies. Clin Dermatol 2013;31:780-6.
Margesson LJ. Practice Gaps "Down There": Failures in Education, Physical Examination, Recognition, Diagnosis, Therapy, Follow-up Care, and Cancer Surveillance in Lichen Sclerosus. JAMA Dermatology 2013;149:1203.

Systematic reviews

Chi CC, Kirtschig G, Baldo M, Brackenbury F, Lewis F, Wojnarowska F. Topical interventions for genital lichen sclerosus. Cochrane Database Syst Rev 2011;12:CD008240.
Chi CC, Kirtschig G, Wojnarowska FT. Systematic review of topical interventions for genital lichen sclerosus. Br J Dermatol 2011;165:39-40.
Chi CC, Kirtschig G, et al. Systematic review and meta-analysis of randomized controlled trials on topical interventions for genital lichen sclerosus. J Am Acad Dermatol 2012;67:305-12.

Randomized controlled trials on topical interventions for LS

Bracco GL, Carli P, Sonni L, Maestrini G, De Marco A, Taddei GL et al. Clinical and histologic effects of topical treatments of vulval lichen sclerosus. A critical evaluation. Journal of Reproductive Medicine 1993;38:37-40.
Cattaneo A, De Marco A, Sonni L, Bracco GL, Carli P, Taddei GL. Clobetasol vs. testosterone in the treatment of lichen sclerosus of the vulvar region [Clobetasolo vs testosterone nel trattamento del lichen scleroso della regione vulvare]. Minerva Ginecologica 1992;44:567-71.
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Patient support groups Lichen sclerosus

UK:
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Summary table 1: Responses achieved by different treatments

Treatment	women	men	girls	boys	extragenital	Long-term
Topical						
Steroid	Clobetasol propionate 75% improved after 3m; complete reversal of signs in 20% (1+ / A) (up to 70% case series)	Clobetasol propionate 76% improved after Ø 7wks (cure claimed in 50% after 3 months treatment)	Clobetasol propionate 65% - 100% improved; complete reversal of signs in 20% - 70% (55% are without continuous treatment)	Mometasone 41% improved after 5 wks (1+/2+ B) (no good study of Clobetasol propionate for 3 months available)		Long-term application needed in some: safe and effective (1+ / A)
Steroid injections	Rx resistant LS 80% improved after Ø 4 inj. (1+ / B)		No reports	Preputioplasty & injection 80% cure		
Oestrogen	No effect	No reports	No reports	No reports	No reports	
Testosterone 2%	20% improved (1+ / A)	No reports	No reports	No reports	No reports	
Progesterone 2% (or 8%)	10% (to 60% case series) improved (1+ / A)	No reports	Pruritus improved in 1 case	No reports	No reports	
Ciclosporin	20% improved (3 / D)	No reports	No reports	No reports	No reports	
Tacrolimus 0.1% or 0.03%	36% complete response, 29% partial (after 24 wks) patients <50 responded better (2+ / C)	Max. 36% complete response, 29% partial (after 24 wks) probably lower (2+ / C)	Tac. 0.03% complete response in 79% after 10 m (maintenance Rx necessary) (3 / D)	Used after surgery; 2/20 relapsed (3 / D)	Plus UV light effective	Effective and safe as maintenance
Pimecrolimus 1%	70% complete, 25% partial relief of symptoms (pruritus) after 3 m; Clobetasol more effective reducing physical	No report?	Effective in majority (relief of itch); no effect on sclerosis (3 / D)	No report?	No report?	

	signs (1+ / B)					
Retinoids	50-60% complete 20-30% partial (3 / D)	No reports	No reports	No reports	No reports	
Calcipotriol	No report	No reports	No reports	No reports	1 case good effect	
Oxatomide	Relief of pruritus (3 / D)	No reports	No reports	No reports		
Moisturizer	10% improved (2+/3 / D)	No reports	No reports	None improved		Maintains symptom relief after steroids
Dermasilk	Fewer symptoms compared to cotton briefs (2+ / D)	No reports	No reports	No reports		
UV1 light	Some effect	No reports	No reports	No reports	Effective (1+ / B)	
PDT	Some effect / pain (3 / D)					
Systemic						
Glucocortico-steroids	No reports	No reports	No reports	No reports	Pulsed steroid & MTX effective	
Retinoids	Effective in 35-85% for different features (1+ / B)	Effective in 35-85% for different features (1+ / B)	No reports	No reports		
Cyclosporine	Effective (3 / D)	No reports	No reports	No reports	No reports	
Methotrexate	Effective (3 / D)	No reports	No reports	No reports	Effective	
Hydroxyurea	Effective (3 / D)	No reports	No reports	No reports	No reports	
Fumarate	No reports					
Antibiotics	Some effect					
Sulphasalazine					Some effect	
Vitamin D					Effective 1 patient	

Vitamin A/E	No more effective than moisturizers					
PABA	No better than placebo	No reports	No reports	No reports	No better than placebo	
Surgery						
Surgery	Reserved for complications	90-100% cure* after circumcision; mean follow-up ca. 5 years in retrospective studies (3 / D)	No reports	Nearly 100% cure* after complete circumcision with 1-5 years prospective follow-up (3 / D)	No reports	No good prospective studies
Perineotomy	for symptomatic introitus stenosis (in selected cases): improvement in quality of life in ca. 80-90%; no long term results (3 / D)	n/a	n/a	n/a	n/a	
CO2-Laser division or hydrodissection with reverse V-plasty	for symptomatic clitoral phimosis in highly selected cases (3 / D)					
Stem cells	Further evaluation needed	No reports	No reports	No reports	No reports	
No treatment of LS				No progression without Rx in early LS is observed (3 / D)		

The recommended treatment options are stated in the text

*Cure as defined as no signs and no symptoms of LS for after treatment for LS

Ø: on average