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GUIDELINES

EuroGuiderm guideline on lichen sclerosus—introduction into lichen sclerosus

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Abstract

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

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

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

Results: Ultrapotent or potent topical corticosteroids in females and males, adults and children remain gold standard of care for genital LS; co-treatment with emollients is recommended. If standard treatment fails in males, a surgical intervention is recommended, complete circumcision may cure LS in males. UV light treatment is recommended for extragenital LS; however, there is limited scientific evidence. Topical calcineurin inhibitors are second line treatment. Laser treatment, using various wave lengths, is under investigation, and it can currently not be recommended for the treatment of LS. Treatment with biologics is only reported in single cases.

For affiliations refer to page 1867.

Conclusions: LS has to be diagnosed and treated as early as possible in order to minimize sequelae like scarring and cancer development. Topical potent and ultrapotent corticosteroids are the gold standard of care; genital LS is often a lifelong disease and needs to be treated long-term.

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

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

Some sections of the guideline were adopted from the previous version[2] of the guideline without changes.

INTRODUCTION

Definition of disease

Lichen sclerosus (LS) is an inflammatory skin disease that typically involves the anogenital site where it causes itching and soreness; it may lead to sexual and urinary dysfunction in women and men; however, it may be asymptomatic. First signs of LS are usually a whitening of the genital skin; sometimes, redness and oedema, fissuring, scarring, shrinkage and fusion of structures may follow in its course; it is associated with an increased risk of genital cancer. Extragenital disease occurs in a minority of patients. The course of LS is usually chronic. Treatment remains unsatisfactory, particularly in women as disabling scar formation is common despite treatment.[3-6] There is some evidence that LS in males may go into remission after circumcision; however, good studies are lacking.

Synonyms like kraurosis vulvae, balanitis xerotica obliterans and white spot disease are old terms and should no longer be used. The suffix 'et atrophicus' has been dropped because it is recognized that some cases of LS are associated with a hypertrophic, rather than atrophic, epithelium.

LS has a huge impact on the quality of life of affected patients, and it is important to raise more awareness of this not uncommon disease in order to diagnose and treat it early.[7-9] This guideline aims to highlight potential triggers for LS, offer advice on current treatment options and suggest future research strategies.

Histopathology

A biopsy to confirm the clinical diagnosis is not considered necessary in all instances, particularly if the clinical picture is diagnostic; however, a biopsy at baseline may be helpful.

A biopsy is certainly indicated if there is doubt about the clinical diagnosis, if there is no response to treatment or if a malignancy or pre-malignancy is suspected. In children, a vulval or penile biopsy is not usually performed, because it may be very traumatic for the child and there is no risk of dysplasia or cancer in prepubertal children. It should be reserved for cases with an uncertain diagnosis and for those who fail to respond to treatments.[10] Biopsies in the genital area in particular in children should be performed by a physician with expertise.

A biopsy should be taken from a typical lesion; this is usually an area of whitish appearance (hyperkeratosis, 'pallor' or sclerosis). If this cannot be found, for example, if fissures or erosions are the complaint, a biopsy may be taken at the end of a fissure, often appearing in the interlabial sulcus, or at the edge of an erosion (not from the middle of an erosive lesions), or, for example, at the posterior end of the labia minora if they appear shortened which indicates disease activity.

If no baseline biopsy was taken before treatment, a 3-week pause of treatment is requested for a reliable histological diagnosis. If this cannot be tolerated by the patient, it is essential to inform the pathologist about the type of treatment. Depending on the length and type of treatment, histological features may be altered.

TABLE 1 Wording of recommendations.

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

Typical histological features of an established LS lesion are (Figure 1)

- compact orthohyperkeratosis,
- epidermal atrophy,
- basal cell degeneration,
- dermal hyalinization,
- an interphase dermatitis with a band-like lymphocytic infiltrate, typically underneath the hyalinized, oedematous dermis[11] and
- follicular plugging in hair bearing skin.

Corticosteroid treatment may induce a remission of the hyperkeratosis and a previously existing mild subepithelial sclerosis. It will especially lead to a reduction of the lymphocytic infiltrate, and will therefore alter all features that result from inflammation such as an interphase dermatitis, basement membrane destruction and keratinocyte damage. Anti-fungal treatment, which is often administered in patients with LS because of a mistakenly diagnosed candida infection, may induce a hypersensitivity reaction leading to a psoriasiform reaction pattern of the skin. In such situations, also eczema/dermatitis (atopic or seborrheic), in particular if early LS is suspected, must be considered.

Genital LS is sometimes difficult to distinguish from genital mucosal/erosive lichen planus (LP). However, LP has several pathognomonic clinical and histological features that usually allow a distinction from LS:

- involvement of glycogenated mucosal tissue (oral, oesophageal, vaginal, vestibular vulval mucosa),
- the histological correlate of Wickham striae, pathognomonic for LP, is a focal and circumscribed accentuation of the granular cell layer, often referred to as wedge-shaped hypergranulosis and focal compact hyperkeratosis,
- keratinocyte apoptosis, not seen in LS,
- circumscript, scarring alopecia in scalp involvement,
- typical nail changes (Kirtschig, Gynecologic Dermatology).[12]

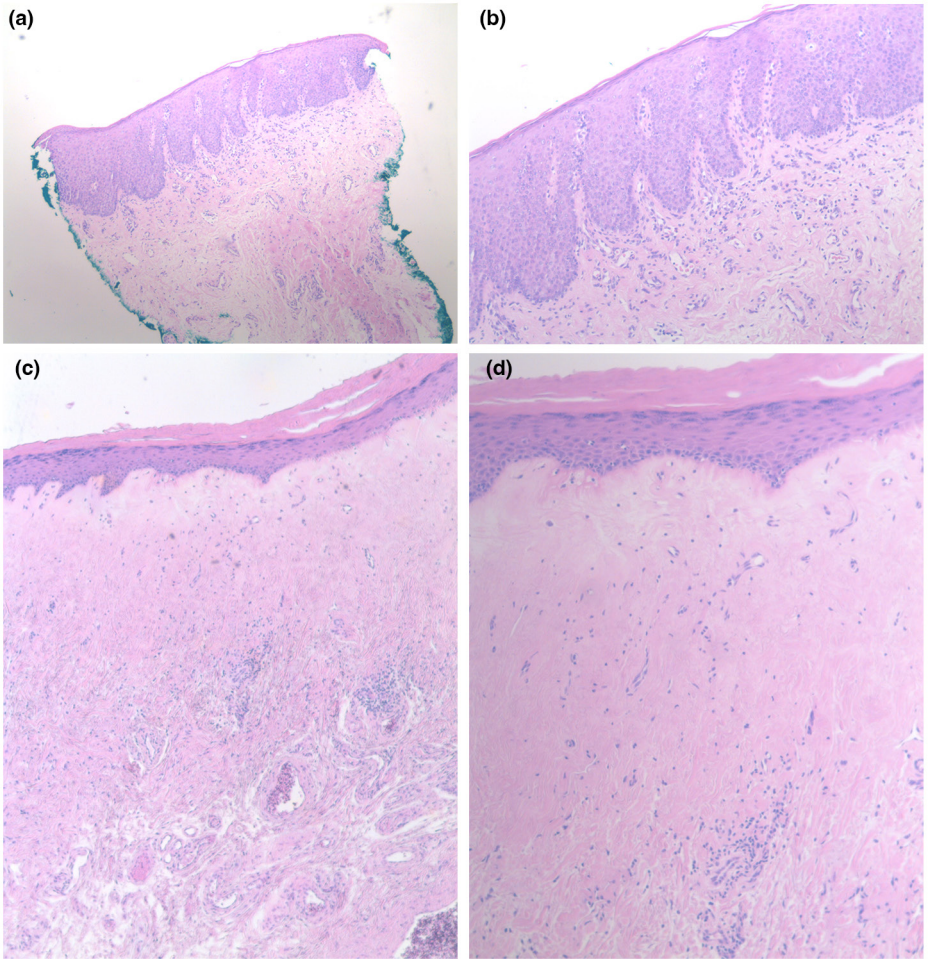


FIGURE 1 Histopathology of early LS in (a, b) (see corresponding clinical Figure 2c), the biopsy was taken from the right interlabial sulcus). Epidermal acanthosis with some hyperkeratosis, rete ridges are broadened. The upper dermis contains a lichenoid lymphocytic infiltrate and is a bit oedematous. Blood vessels are slightly dilated in the upper plexus. Late LS in (c, d) shows an atrophic epidermis, with orthohyperkeratosis, rete ridges are partly elapsed, and there is a broad subepidermal oedema and swollen and homogenized collagen fibres. Blood and lymphocytic vessels are dilated. The lichenoid lymphocytic infiltrate is pushed by the oedema to middermis. We thank Luis Mario Orantes-Aguirre, Unilabs Bern, Switzerland, for the provision of the histological pictures.

Twenty-five years ago, Fung & LeBoit already made an attempt to establish the histological differences between LS and LP, and consensus is still not achieved (Table 2).

Day et al.[14] suggest the following clinicopathologic diagnosis of genital mucosal/erosive LP incorporating 5 criteria: (a) a well-demarcated, glazed red macule or patch at labia minora, vestibule and/or vagina, (b) disease affects hairless skin, mucocutaneous junction and/or non-keratinized squamous epithelium, (c) evidence of basal layer damage, categorized as degenerative or regenerative, (d) a closely applied band-like lymphocytic infiltrate and (e) absent subepithelial sclerosis.

However, it has to be noticed that there is a spectrum of histological and clinical features in LS and in early disease some features seen in established disease are missing. In early LS (Figures 1a,b and 2c), some classical features like the hyalinization of the upper dermis may be lacking and a firm histological diagnosis cannot be made. Attili & Attili made an attempt to establish the various features of early and late LS (Table 3).[15] However, this needs to be confirmed and consented. In any case, histological and clinical features have to be correlated, and sometimes, only time will show how the disease will develop before a firm diagnosis can be made.

TABLE 2 Summary of histological differences between LS and LP established by Fung & LeBoit in 1998[13].

	LS % with stated feature	LP % with stated feature
Psoriasiform lichenoid pattern	100	0
Basilar epidermotropism	78	0
Loss of papillary dermal elastic fibres	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

Also, hypertrophic forms of genital LS and LP may show similar clinical and histological features making a distinction difficult in some cases. Of particular importance is to rule out precancerous or cancerous lesions. Squamous cell cancers (SCC) in LS develop independent of human papilloma virus (HPV) infection. While HPV induced SCC develop slowly over several years, HPV-independent SCC can develop rapidly within several months.[17] Therefore, any new hyperkeratotic lesion or newly arising erosions and ulcerations are suspicious for a HPV-independent vulval intraepithelial neoplasia, also referred to as differentiated vulval intraepithelial neoplasia and should be biopsied.

In conclusion, greater awareness of the clinicopathological spectrum of LS should enable early diagnosis and treatment. A biopsy read by an experienced (dermato)histopathologist is particularly helpful to rule out clinical differential diagnoses such as LP and eczema, atopic or seborrheic, in particular if early LS is suspected, and detect precancerous and cancerous lesions.

Genetic predisposition

A genetic predisposition is implicated. A positive family history of LS is observed between 5.4% and 12% of patients with genital LS in British, Italian and Dutch studies.[18-22] Familial occurrence is probably higher than expected and may be as high as 39%.[19,23]

HLA Immunogenetic studies have demonstrated a significant association with particular HLA class II antigens in patients compared with controls.[24-27] The existence of a susceptibility gene for sclerosis in this region of the MHC is

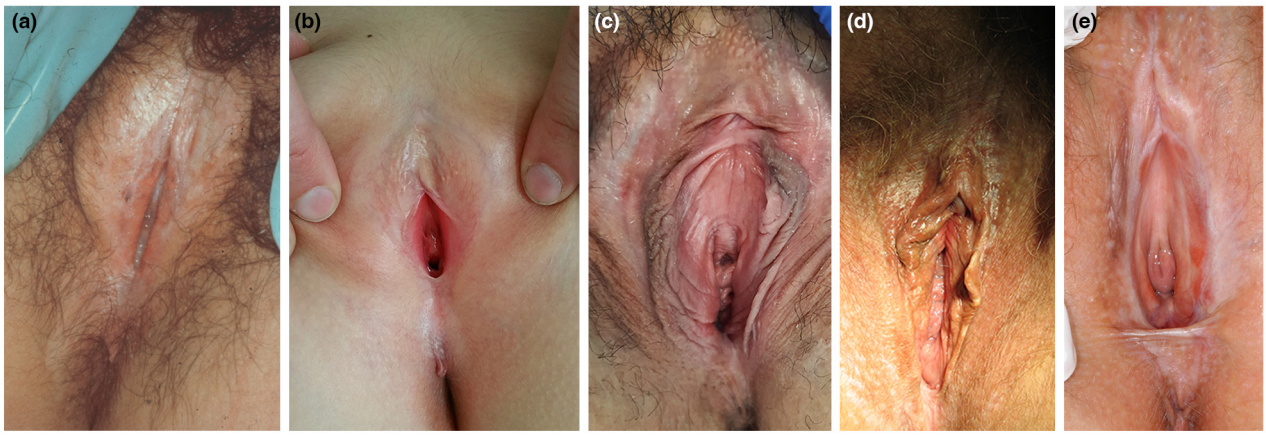


FIGURE 2 (a–e) Lichen sclerosus in two (pre-)pubertal girls showing severe hyperkeratosis around the clitoris and interlabial sulci in (a)[16] and mild hyperkeratosis around the clitoris and posterior fourchette in (b). (c) shows early LS without any sclerotic changes but complaint of itch, fissuring during intercourse and a short left labium minus (corresponding histology see Figure 1a,b). (d) shows white lesions in around the clitoris and possibly posterior fourchette in a woman with LS; and severe hyperkeratosis, fusion above the clitoris resulting in a buried clitoris and regressed/absorbed labia minora resulting in severe architectural changes and an ecchymosis at the left interlabial sulcus, typically seen in LS in (e).

TABLE 3 Histological stages of genital lichen sclerosus (133 cases).[15]

	Early pre-sclerotic phase		Sclerotic phase conventional lichen sclerosus		Atrophic phase
	Stage 1a (17%)	**Stage 1b (27%)**	**Stage 2a (44%)**	**Stage 2b (4%)**	**Stage 3 (8%)**
Epidermis	Psoriasiform	Widening of papillae and loss of rete ridge pattern	Thin and flat epidermis	Pseudo-epithelial hyperplasia	Thin and atrophic
Basement zone	Vacuolar/ lichenoid interface dermatitis with an indistinct basement membrane	Diffuse dermal lymphocytic infiltrate with thickened or multi stranded basement membrane	Thickened basement membrane merging with hyalinized papillary dermis. Focal basilar lymphocytic infiltration	Diffuse vacuolar change with basilar infiltration of lymphocytes	Thin basement membrane. No inflammatory cells
Papillary dermis	Normal	Patchy peri vascular lymphocytic infiltrates. New capillaries with thicker walls	Loss of normal structure with hyalinization and sclerosis	Loss of normal structure with hyalinization and sclerosis	Normal structure replaced by loose matrix of fibrosis. Negligible inflammatory cells
Reticular dermis	Normal	Normal	Mid-dermal band of lymphocytic infiltrate along with thick walled and dilated blood vessels	Structural loss with hyalinization and sclerosis	Loose matrix of fibrosis. Negligible inflammatory cells

underlined by the finding that the same region is associated with an increased risk of autoimmune diseases in women.[28]

LS is described to occur in individuals with Turner syndrome (X0 chromosome) and with a Fitzpatrick phototypes 1 and 2 in boys.[29] The association of Turner syndrome and LS leads to speculations of the influence of low oestrogen; Turner syndrome is also associated with an increased risk of immune mediated inflammatory disease, such as autoimmune thyroiditis, coeliac disease, type 1 diabetes mellitus, inflammatory bowel disease, alopecia areata or vitiligo. The presence of isochromosome iXq and exposure to oestradiol may contribute to the development of the autoimmune process.[30-32]

Gene expression pattern of LS in males using DNA microarray functional 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.[33]

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.[34] TGF-ß/Smad-3 independent up-regulation of CTGF may induce accumulation of ECM proteins and maintain fibrosis in chronic vulval LS.

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.[35] Hypermethylation of the promoters of genes like IRF6 and RAR β, with their subsequent down-expression, seems to play a role in vulval LS progression towards cancer.[36,37] The involvement of an aberrant methylation of the promoters of these and other genes in the pathogenesis of vulval LS is less evident.

Immunological findings

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.[38]

Pilatz et al. investigated the cellular composition, inflammatory infiltrate and microenvironment in boys with congenital phimosis and LS. They found distinct expression patterns of tissue remodelling 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.[39]

Kaya et al. described that CD44-targeted deficiency in mouse epidermis results in a LS-like histological picture.[40] In human genital and extragenital LS lesions, the epidermal expression of CD44 is decreased or absent, both at the protein and mRNA levels, which is correlated with an accumulation of hyaluronate in the superficial dermis. This suggests that LS might result from an epidermal damage of unknown origin, responsible for a progressive decrease in keratinocyte CD44, subsequently leading to dermal changes

in which hyaluronate accumulation is a conspicuous feature.[41] 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.[42]

Tchorzewski et al. describe that the involution of lichen sclerosus-affected tissues may be the suppressive effect exerted by CD4+CD25+ suppressor T lymphocytes, the increase in IL-10 inhibitory cytokine production, and diminished granulocyte ROI production. Inflammatory infiltrates in the affected regions of the skin are characterized by a diminished number of CD3 lymphocytes bearing the CD26 molecule, which may be responsible for an autocrine defect in bioactive mediator degradation.[43]

The dysregulation of certain mediators, like Dkk-1, GDF-15 IGFBP-2 and CHI3L1, involved in both inflammatory processes and collagen metabolism in keratinocytes and fibroblasts obtained from vulval LS samples have been identified by Corazza et al. Both keratinocytes and fibroblasts seem to actively participate in this process, with peculiar and in some way different profiles of mediators' release.[44,45]

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;[46-49] however, it may be a secondary phenomenon.

Interestingly, the clinicopathological phenotype of lipoid proteinosis, which results from mutations in ECM1, resembles LS.[46] However, the pathogenic relevance of these findings needs further investigation.

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.[50]

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.[51]

Oxidative stress, which is involved in the pathogenesis of several autoimmune and malignant disorders, may contribute to these processes in LS.[52] 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.

Associated diseases

Immune mediated inflammatory diseases like thyroid disease (most common), vitiligo, alopecia areata, autoimmune bowel disease, rheumatoid arthritis, primary biliary cirrhosis, pernicious anaemia, localized scleroderma/morphoea, systemic lupus erythematosus, frontal fibrosing alopecia[53] 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%).[24,26,54,55,56,57,58,59,60,61,62,63,64]

The prevalence of psoriasis (Th1 response) in vulval LS patients was found to be higher than in the general population and among non-LS patients.[65,66]

Atopic dermatitis (Th2 response) was found more commonly in boys with LS compared to circumcised boys without LS.[67,68] In male patients, LS is associated with an increased body mass index and has been associated with coronary artery disease, diabetes mellitus and tobacco use.[69,70]

Diabetes mellitus (DM) and LS are more frequently reported than expected, some recommend DM screening in LS.[21,71]

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%) (2 to 3-fold increased risk),[72] fibromyalgia (9.1%), temporomandibular joint disorder (13.0%) and vulval pain (83.1%).[73] A multicentre Italian study evidenced that metabolic factors (obesity, hypertension, hypothyroidism and a sedentary lifestyle) may play a role in genital LS pathogenesis in genetically predisposed patients, and that risk profile is similar in males and females.[22,70]

Hu et al. compared the demographics and self-reported medical comorbidities of patients with vulval LS ($n = 865$) with those of women with other vulval conditions ($n = 1118$). Increasing age, thyroid disease and anorectal fissures were significantly associated with vulval LS. The association between anorectal fissures and vulval LS likely represents a sequela of the disease rather than a true comorbidity.[62]

The association of genital melanoma and LS is described in several case series, mainly in women.[74] Vulval melanoma is rare, with an incidence of 0.10–0.13 per 100,000 individuals, presenting typically in postmenopausal women. There seems to be an increased incidence of vulval melanoma among patients with LS, also in girls![75] The increased risk of vulval melanoma and SCC should be noted in patients with LS.

EPIDEMIOLOGY

Incidence/prevalence

The exact prevalence of LS is unknown and is probably underestimated, possibly because LS is underdiagnosed.[76,77] It is a disease commonly seen in 'vulval' and 'penile' clinics. Together with spongiotic dermatitis and other lichenoid

interface dermatoses, it counts for the majority of specimens in pathology departments investigating foreskins.[78]

The suspected prevalence varies between 0.1% and 3% for children and old women (>80 years), respectively.[76,79,80,81] Extrapolation from the Oxford clinic data suggests that approximately 150–200 women per million population present each year.[82] A recent study determined an incidence of LS in women by age 80 of 1.6%.[83] The incidence in males was estimated to be 0.07% according to retrospectively reviewed discharge records at an US Army Medical Centre.[84]

Age at onset

LS can occur at any age. The prevalence of vulval LS increases with age, women after the menopause are most commonly affected, which may not necessarily be linked to the postmenopausal status.[21,81] However, in about 20% of the women the onset of disease is premenopausal.[85] A second peak is thought to occur before puberty[86]; both peaks are in the nonreproductive years and are associated with low oestrogen levels. It could be that a low oestrogen level has an aetiological role 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 (Koebner phenomenon). However, Wallace described a continuous increase in incidence from puberty to perimenopause peaking around the menopause with decrease thereafter. In men, the incidence seems to increase after puberty, with possibly a prepubertal peak, and decreases again in older age (>60 years).[81,84,87,88,89] 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[84] but a peak around the third decade is also observed in a non-military setting.[87]

Sex ratio

Women seem more often 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.[60,80,81,89,90,91,92,93,94]

CLINICAL PRESENTATION AND SEQUELAE OF DISEASE

LS is a chronic disease with waxing and waning symptoms. Itch or pain is the main initial complaint in genital LS in women and sexual and urinary dysfunction in men.[95]

Females

The characteristic sites involved in females are the interlabial sulci, labia minora, clitoral hood, the posterior fourchette, perineal body and perianal skin (often in girls) (Figure 3). Labia majora and the urethral meatus may be affected in rare cases.

Males

LS in men and boys usually occurs on the glans penis, coronary sulcus, urethral meatus and/or foreskin, with a predilection for the perifrenular area (Figure 4), and may cause phimosis in a previously retractable foreskin or adhesions of the foreskin to the glans causing dysuria or painful erection. Acquired (secondary) phimosis in males is highly suspicious to be caused by LS. Rarely, the penile shaft, perineal, scrotal and perianal skin are affected. 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 shortly after birth.[87,96]

Extragenital LS

LS of the extragenital skin alone is rare and has been reported in about 6% of all affected women.[81] Involvement of the scalp, including bullous variants and scarring alopecia, is rare but reported.[97-99] It is generally taught that LS does not affect the oral mucosa, nails or vagina; however, the occurrence at these sites is reported.[90,100,101,102,103,104]

Symptoms of LS

Women and girls commonly report itching, burning pain and anal or genital bleeding due to fissuring of the affected tissue. Women also report painful, less pleasurable or even impossible sexual intercourse due to stenosis and scarring. Painful defecation may be a problem (because of fissures), especially in girls, causing constipation. Soft stools after a fibre rich diet may help. Children may also present with gastrointestinal complaints, besides constipation, regulation of the nutrition and defecation may help.

Signs of LS

The primary lesions on the skin are flat ivory-coloured spots (Figures 2c and 5), which may merge together into crinkly thin (skin atrophy) or hyperkeratotic patches (Figures 5 and 6b). On the vulva or penis, there may be oedema, an erythema adjacent to hypopigmented spots (either hyperkeratotic; Figure 6b or sclerotic) and fissures. Purpura or ecchymoses are typical and harmless but for some patients distressing features of LS. Scarring is common and is observed in about 80% of women and 30% of girls with LS.[5] It may lead to loss and agglutination of the labia minora, possibly midline fusion with fusion of the clitoral hood burying the clitoris and narrowing and rarely obliteration 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.

The Koebner phenomenon that describes the development of lesions in previously normal looking skin after scratching or other trauma is well recognized.[81]

Symptoms

- Itch (mainly in genital LS in females)
- Pain/Soreness
- Burning
- Irritation
- Feeling of dryness
- Dysaesthesia
- Constipation, in perianal involvement, particularly in girls
- Dyspareunia or apareunia (disturbed sexual functioning)
- Dysuria (pain, disturbed urinary stream)
- Urinary bladder pain (abacterial cystitis)
- LS can be asymptomatic

Signs

- Oedema (swelling of the skin)
- Slight erythema (redness)
- Hyperkeratosis (white thickened skin; hyperkeratosis on histology)
- Sclerosis (tight, yellowish white skin, for example, resulting in phimosis; dermal hyalinization on histology)
- Pallor (pale, whitish areas; the histological correlate is not described)
- Atrophic skin (crinkly skin; epidermal atrophy on histology)
- Fissuring (skin fragility, loss of elasticity leading to splitting of skin)
- Erosions
- Blistering is very rare
- Ecchymoses/purpura is common in genital LS (due to fragile, sclerotic and ectatic blood vessels)
- Changes may be localized to the vulva or include the perianal area, forming a 'figure-of-eight' distribution

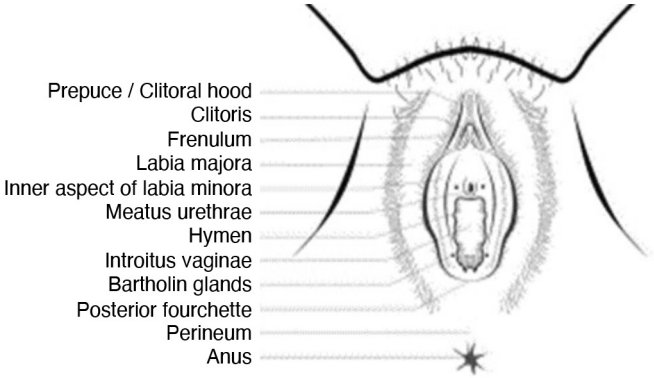


FIGURE 3 Graph of female external genitalia adopted from Gynecologic Dermatology.[12]

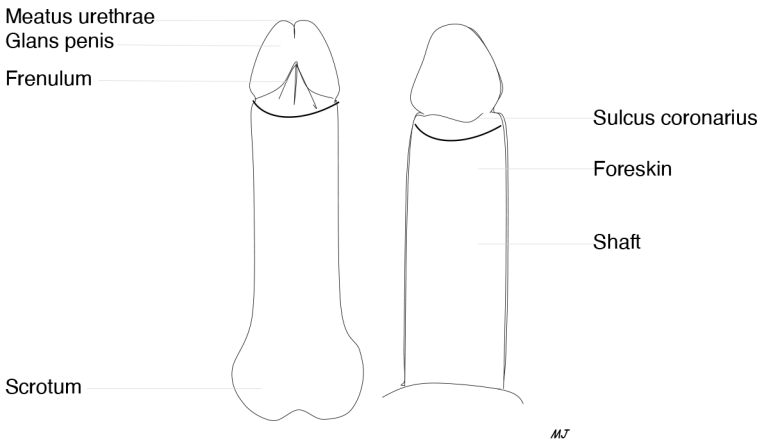


FIGURE 4 Graph of penile structures.

- Scarring may lead to architectural changes (e.g., resorption of the labia minora, fusing in the midline with burying, but not loss of the clitoris in women and, e.g., phimosis, a narrow meatus urethrae and a sclerotic frenulum breve in men)
- Follicular plugging (in extragenital LS)
- Post-inflammatory hyperpigmentation is not a common finding, but rather points towards the diagnosis of lichen planus

Physicians should be familiar with the various signs of LS. Some of the signs represent early, reversible signs others are permanent, non-reversible signs of LS

- Fissures/erosions are longitudinal/patchy ruptures of the skin surface.
- Ecchymoses are bleedings within the skin.
- Hyperkeratoses are patches/plaques of bright white skin with a 'powdery' appearance.

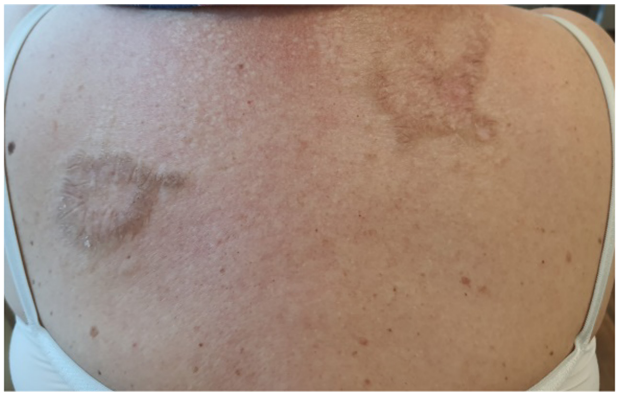


FIGURE 5 Porcelain like and hyperkeratotic LS at the back.

IMPORTANT: Hyperkeratoses must be distinguished from

- Sclerosis that are areas of yellowish/ivory white skin with a smooth/waxy/firm texture
- Pallor that are areas of pale whitish skin that differ from hyperkeratoses in that they are not 'powdery'. Sclerosis and pallor are usually permanent signs of genital LS, histological correlates need to be defined.

Complications

- Loss of self-esteem (e.g., concern about the genital appearance)
- Impaired quality of life
- Development of anogenital carcinoma (actual risk <5%)
- Development of clitoral pseudo-cyst
- Sexual dysfunction
- Urinary dysfunction
- Genital dysaesthesia

Mental health disorders are an underestimated complication of chronic genital diseases.[105] LS is shown to have a profound effect on mental health.[105] Parygina et al. report that mental health disorders were diagnosed in 22 (66.7%) patients with chronic vulval disease.[106] Mixed anxiety-depressive disorder and depressive episodes were diagnosed most frequently—in 36.4% and 22.7% of patients, respectively. The most significant risk factors for mental health disorders were duration of the disease and itching, followed by the severity of itching according to visual analogue scale (VAS) and itch severity scale (ISS). In addition, high scores of VAS regarding the effect of dermatoses on the quality of life are a risk factor for the formation of mental disorders. Sexual dysfunction, dysmorphology and affection of genital area were less important risk factors for mental health disorders. Patients with these predictors are recommended to consult a psychiatrist.

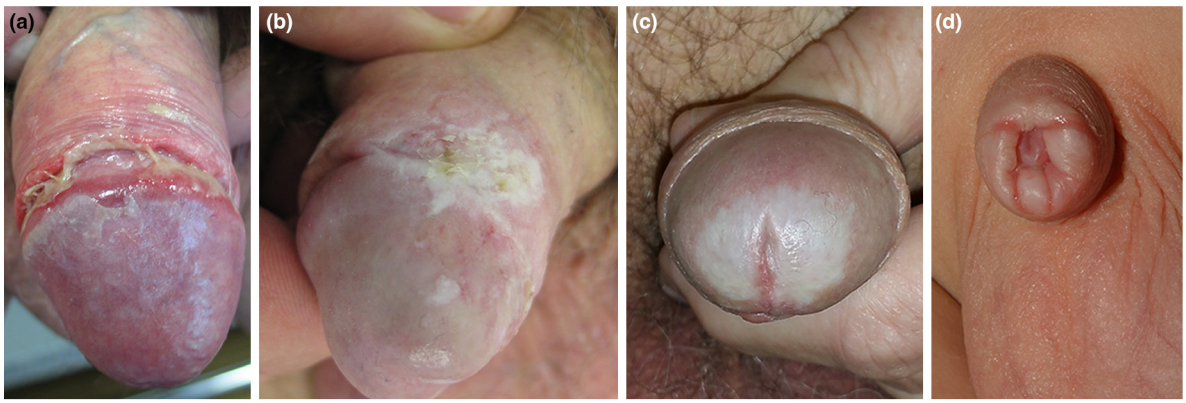


FIGURE 6 LS in males, (a) erosive LS at the sulcus and white lesions at the glans, (b) hyperkeratotic plaque at the sulcus, (c) pallor or sclerosis at the glans with the meatus affected by LS and (d) secondary phimosis in a boy.

TRIGGER FACTORS

There are hardly any high quality studies reporting potential triggering factors or risks for the development of LS; however, the following aspects are mentioned in the literature and require further investigation.

An increased risk of developing LS is described under the following circumstances:

Trauma

The appearance of new skin lesions on previously unaffected skin secondary to trauma is observed in LS (Koebner phenomenon).

Pelvic surgery, manoeuvres of the foreskin "mechanical reduction of the foreskin" performed at least 5-10 times per month and genital injury are thought to trigger LS in genetically predisposed individuals.[6,21,29,58,107]

Baykal et al. describe development of LS on the sites of striae distensae and a surgical scar in a patient with coexistent morphoea.[107] In a large series of paediatric LS, associations with trauma, autoimmunity, and infection were noted. LS may be associated with sexual abuse, possibly due to genital trauma.[108,109]

Parental status

Parous women were at higher risk compared to nulliparous women.[110,111] This finding was not significant when only married women were considered.[110]

Radiotherapy

Radiation-induced LS of the vulval region is reported after radiation for vaginal cancer.[112,113]

Urine

The relevance of urine in the pathogenesis of LS is supported by several observations and studies; the exact mechanism of how urine may act in individuals with a probably genetic predisposition to LS has to be further investigated.[114-120] Gupta et al. reported six patients (three males and three females) with histologically-proven LS that showed relative sparing of the uncovered areas of the genitals, thereby suggesting that the occlusion of the genital skin may be playing a greater role in the causation of LS than is currently thought, in both sexes.[114]

A case series further strengthens the urinary occlusion hypothesis for the causation of male genital LS. It is important to recognize that urological interventions can create incompetence of the naviculomeatal valve post voiding. In uncircumcised men, this creates a risk factor for male genital LS that was not previously present. Occlusion the phenomenon of Koebnerization and currently unelucidated epithelial susceptibility factors lead to inflammation, sclerosis and cancer. Patients and urologists should be aware of these possibilities and preventative measures instituted, for example, adaptive voiding habits and barrier protection.[120]

Furthermore, a broken barrier function of the skin in atopic individuals may increase the risk factor 'urine'.[67,121]

Infections

Various genital infections are debated to be a trigger for LS. Vulvitis and urethritis were associated with LS in one study;[111] however, this was not confirmed in another.[21]

Borrelia burgdorferi

The hints towards Borrelia burgdorferi as a trigger in LS are impressive and accumulating but remain conflicting.

Using focus-floating microscopy, Eisendle et al. detected Borrelia species in 38 of 60 cases (63%) of LS and in 61 of 68 (90%) of positive controls of classic borreliosis, but Borrelia species were absent in all negative controls. Borrelia species were detected significantly more often in early inflammatory-rich (31 of 39 [80%]) than in late inflammatory-poor (7 of 21 [33.3%]) cases ($p = 0.001$). Polymerase chain reaction findings were positive in 25 of 68 positive controls (37%) and negative in all 11 cases of LS and all 15 negative controls.[122]

Furthermore, investigations by Aberer et al. support the hypothesis that some Borrelia species enhance collagen mRNA expression and can stimulate growth factors responsible for increased collagen production.[123]

There are few reports about antibiotic treatment in LS; however, doxycycline, penicillins and cephalosporines were successfully used.[98,124,125] This warrants further studies.[122,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153]

Mycoplasma

Mycoplasma infection is thought to be a potential cofactor in LS.[154,155]

Both PCR and ELISA proved a significant presence of Mycoplasma when compared to controls in patients with LS (PCR positivity: 48/51 vs. 12/40, $p < 0.01$; ELISA positivity 22/40 vs. 5/26, $p < 0.01$), while only PCR data showed significant difference between morphoea patients and controls (17/20 vs. 12/40, $p < 0.01$): these cases had no significant Mycoplasma antibody positivity.[155]

Viral infections

Pilatz et al. provided evidence that HPV is usually not present in the foreskin of boys with persistent phimosis after their first year of life and that topical glucocorticoid treatment failure is not associated with HPV or any specific histopathological changes (LS). These results showed no relationship between HPV and LS and are in accordance with the literature.[156-159]

Epstein–Barr virus was found in a preliminary study; the follow-up will elucidate whether EBV could play a role in LS. Hepatitis C virus infection and *Helicobacter pylori* are described in single reports to be associated with LS.[160-162]

Microbiome

Alterations of the microbiome may also play a role in the development or chronic course of LS. There are recent studies that demonstrate the role of a dysbiosis in the pathogenesis of LS and correcting the composition of the microbiome may be applicable in supplementary LS therapy by targeting the restoration of the beneficial flora.[163-167] Interestingly, urinary infections and use of absorbents (panty liners) are also reported to be more common in symptomatic LS patients.[168]

Psychological factors

Genital LS has an enormous impact on the patient's psychological and sexual wellbeing. There are some studies that investigated the topic and usually highlight the impact of LS on the patient's quality of life; the psychological constitution as a risk factor is, for example, studied by Grasso et al.[169-171]

Grasso et al. investigated anxiety as risk factor for vulval LS and describe that women ($n = 25$) suffering from LS already have a psychic labile condition with an anxiety degree that will impact on the variability and the progress of LS and could have a causal role in the development of the disease.[169]

Hormones

Data by Günthert et al.[172] suggest that disturbance of the androgen dependent growth of the vulvar skin by oral contraceptive pills (OCP) and especially by OCPs with antiandrogenic properties might trigger the early onset of LS in a subgroup of susceptible young women.

BMI/DM/CAD/smoking

People with a family history of diabetes mellitus (DM) and men with elevated body mass index (BMI), diabetes mellitus, coronary artery disease (CAD) and smoking were at increased risk of developing LS.[21,70,93,173]

Development and chronicity of LS may not be a purely dermatologic condition, but may be associated or confounded by systemic disease or vascular compromise like CAD, DM and smoking.

Also, Virgili et al. found that overweight and obesity, blood hypertension, hypothyroidism and an educational attainment equal or above upper secondary school level were more frequent among the study patients with LS than among the general Italian population. Moreover, a family history of genital LS was reported more frequently than expected among patients with genital LS. These factors were similar in males and females. The disease tended to occur later in females than in males.[22]

However, Sideri et al. were not able to support this hypotheses, as no difference was observed in their distribution of cases and controls with reference to education, smoking habits, body mass index and previous history of diabetes.[110]

Buried penis has been reported as a trigger on several occasions, as has risk of recurrence of LS after surgery in obese males.[174-178]

Food

Multiple conditional logistic regression analysis showed that vulval dystrophy was positively associated with eating hot (spicy) food (OR = 2.55, 95% CI: 1.24–5.25), mood (OR = 4.27, 95% CI: 1.96–9.29), order of pregnancy (OR = 3.37, 95% CI: 2.11–5.40), vulvitis (OR = 6.74, 95% CI: 2.66–17.09) and urethritis (OR = 11.02, 95% CI: 1.01–120.19).[111]

Eating pork is reported to possibly worsen symptoms of LS.[168]

Medication

A study by Alharbi confirms the association between Immune Checkpoint Inhibitors (ICIs) and LS and lichen planus.[179] Corticosteroid (local/systemic or both) and calcineurin inhibitor treatment might improve patients' pain and prevent the progression of adverse events. In addition, some cases require ICI cessation to achieve complete remission. Finally, LS and lichen planus should be included as a part of the immune-related side effects of checkpoint inhibitor medications.

Protecting factors

There was no association between retinoids and risk of vulval LS, but intake of carotenoids was inversely and strongly associated with vulval LS.[110]

DIAGNOSIS

The diagnosis of LS is usually made according to the characteristic clinical appearance. In typical cases, a biopsy may

not be needed, but many clinicians prefer to take a biopsy at presentation. In children, a biopsy of genital skin is not usually performed, because it may be very traumatic for the child. A biopsy should be performed if the clinical diagnosis is uncertain, dysplasia/carcinoma is suspected or if there is failure of first line treatment, also in children.[10,180]

Clinical and pathological correlation is essential. In early disease, histology can be non-specific.

Further investigations

Investigation for autoimmune disease should be done if clinically indicated, because some diseases (e.g., thyroid disease, pernicious anaemia, vitiligo and diabetes mellitus) are associated with LS in females.[55] These conditions may be asymptomatic. Skin swabs for bacterial, fungal or viral infection are only useful to exclude co-existing infection, if there are symptoms or signs suggestive of this. Patch testing, an epidermal test on the back to prove a contact allergy, is rarely required and only if secondary (medicament) allergy is suspected. The advice of a dermatologist should be sought.

LS in children

Special attention has to be paid to children with anogenital disease, and it has to be kept in mind that children are not 'little adults'.

A child friendly setting must be created. Talking about anogenital problems may be even more difficult for children than for adults. Children should be accompanied by a person they trust and they should be allowed and encouraged to talk about their complaints in their own words.

A safe environment needs to be created. The investigation of the anogenital site should be performed by an experienced physician who knows the disease, the anatomy of the genitals in children and who knows how to deal with children.

The investigation of girls should not be performed using a gynaecological chair, as this may humiliating and may cause anxiety, an examination table is more appropriate. Explain what you are about to do and ask the child for its consent.

If the clinical picture is not diagnostic and you consider a biopsy weigh the pros and cons. Sometimes, a second visit after a few months' time will offer a clearer picture, or discuss the case in an interdisciplinary team, or refer to an experienced colleague. A biopsy is the ultimate action and should be avoided whenever possible.

Explain the disease and its treatment in words the child is able to understand, demonstrate where ointments need to be applied and explain the importance of long-term follow-up.

DIFFERENTIAL DIAGNOSES

Mucosal or erosive lichen planus is the main differential diagnosis. Inverse psoriasis, eczema/lichen simplex, non-specific balanoposthitis, vitiligo (particularly difficult in children), morphoea, graft-versus-host disease (GvHD), autoimmune bullous diseases, plasma cell vulvitis/balanitis, Paget disease, lSIL/hSIL and SCCs may show clinical features resembling LS. If the diagnosis is in doubt, a biopsy has to be performed.[181] For more information on diseases that need to be differentiated, the IUSTI guideline may be consulted.[182]

One interesting case report describes an erosive vulvovaginitis, histologically not compatible with LS or lichen planus but associated with an intralesional Borrelia burgdorfei infection, it resolved after 5 months of treatment with topical clindamycin and oral doxycycline.[141]

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

FEATURES OF EXTRAGENITAL LICHEN SCLEROSUS

In contrast to genital LS, extragenital disease is much less frequent, and it affects approximately 10%–20% of patients with LS.[6] It predominantly occurs in women, with a reported female/male ratio of 7:2.[183] Extragenital LS without concomitant genital disease is very rare. Extragenital LS and morphoea share clinical similarities, and intraindividual coexistence of both conditions is reported.[184] Clinically, extragenital LS appears as porcelain-like polygonal papules or plaques (Figure 5). Several morphologic variants have been reported for extragenital LS, including bullous, ulcerative, annular, desquamative, teleangiectatic, angiokeratomatous, verrucous and vitiligoid LS.[183] In bullous extragenital LS, blister formation might be explained by two mechanisms. Firstly, stability of the basal membrane zone is disrupted by interface dermatitis-induced liquefaction degeneration of the basal layer. Secondly, oedema of the papillary dermis disrupts the collagen fibres and flattens the rete ridges.[185] The majority of lesions are asymptomatic or accompanied by mild itching. In widespread extragenital LS affecting several anatomical sites, cutaneous atrophy and sclerosis might cause substantial discomfort. Extragenital LS can affect the entire body, but predisposed anatomical sites include the trunk (sub-mammary, abdomen, buttocks, shoulders, wrists and chest) and proximal extremities.[186] The head (e.g., eyelids, forehead or scalp) is rarely affected.[187-189] Bullous LS is predominantly located in sites that are prone to trauma, for example, the belt region. Blister formation in extragenital LS can become haemorrhagic and may lead to superficial erosions and complicating secondary bacterial or fungal infections.[190] The Koebner phenomenon is a recognized feature of extragenital LS. Scarring, trauma or tattoos have been reported in association with extragenital LS.[191,192]

PATIENT EDUCATION PROGRAMS

We **recommend** that patients are educated and followed up by a physician experienced in lichen sclerosus.	↑↑	100% agreement (16/16) Consensus-based
We **recommend** that lichen sclerosus patients are guided and supported in dealing with lichen sclerosus in daily life and sexual health.	↑↑	100% agreement (15/15) Consensus-based
We **recommend** that lichen sclerosus patients are made aware of patient organisations and their offers, if available.	↑↑	100% agreement (16/16) Consensus-based
We **recommend** that lichen sclerosus patients receive information regarding the anatomy of the affected sites.	↑↑	100% agreement (16/16) Consensus-based
We **recommend** providing a written information and online information, e.g. information brochures or flyers to lichen sclerosus patients.	↑↑	100% agreement (16/16) Consensus-based
We **recommend** that lichen sclerosus patients are specifically educated about the benefits and safety aspects of each treatment option proposed.	↑↑	100% agreement (16/16) Consensus-based
We **recommend** that lichen sclerosus patients are motivated and guided to perform self-examinations.	↑↑	100% agreement (16/16) Consensus-based

LS is a chronic disease which can have significant complications that affect quality of life including sexuality. It is necessary for patients to be educated so that they can effectively manage their condition. Patient organizations meet these needs for some patients; a new development are patient education programs offered at hospitals.

We recommend the following minimum standard of patient education:

Minimum standard of patient education

Information and guidance for patients with LS are important and indispensable and should be continued throughout diagnosing and treating LS. There will be different phases with different accents, and repeated information helps to understand what happens.

- Diagnosis. Usually, the LS diagnosis is made by a physician taking the patient's history and examination.
  - When examining the patient, always provide the patient a hand mirror so that you examine the anogenital area together, and explain what you see: signs/changes caused by LS.
  - At the time of diagnosis, most patients are overwhelmed and not able to focus and concentrate. Explain at least: LS is a chronic, inflammatory disease, affecting mainly the anogenital site. The gold standard of treatment is topical corticosteroids.
  - A short-term follow-up appointment after diagnosing will give the patient a chance to pose further questions and supports compliance. Offer the patient to bring an accompanying person to the appointment.
- Anatomy. Most patients don't know much about the genital anatomy. In order to treat themselves properly, patients need to get informed about their anogenital region.
  - Male patients: Mostly the foreskin, frenulum, glans and urethral opening are affected, in rarer instances the urethra. Explain that the foreskin and the meatus can become tight causing problems when urinating and during sexual activities. Use a drawing or picture to explain.
  - Female patients: Make a drawing of the vulva and explain the different parts, such as labia minora and majora, urethral opening, clitoris and clitoral hood, introitus and hymenal parts, perineum and anus; see chapter diagnosis of the guideline. Explain that the clitoris can become covered by the clitoral hood. Show a drawing of the clitoral body and explain, that most of the clitoral complex is internal, and that sexual stimulation of the clitoris remains possible.
- The disease LS. Every patient needs to be informed and educated about symptoms and signs of LS, potentially irritating factors (cleaning habits, cloths, micturition/voiding, defaecation and intercourse), the chronic nature of LS, the potential progression of the disease and the importance of self-examination. So, it is important to explain to every patient:
  - The most frequent anogenital complaints are itching in females and pain in males.
  - Skin in anogenital LS can become fragile, eroded, thickened and/or sclerotic and may bleed.
  - Urination and defecation can be(come) painful (irritating). Rinsing with a bottle of water during urination will dilute the urine and make urination more comfortable.
  - Alternatively, the skin may be protected with some greasy ointment, for example, Vaseline, before urination, defaecation or taking a shower.

- Hypertonia of the pelvic floor muscles as a result of pain can worsen micturition/defaecation and sexual penetration in females.
- Avoiding mechanical triggers like tight clothing or hard bicycle saddle can help to reduce the pain.
- Provide written information, for example information leaflets from patient organizations.
- Point out meaningful websites*with information from a patient association.

- Treatment of LS. LS seems to be rather under- than over treated.[193] With the help of good information and education about the use of topical corticosteroids (TCS) adherence to therapy can be promoted. Inform your patient about the following:
  - Potent or ultrapotent TCS (see chapter treatment in the second part of the guideline) are the first-choice treatment to suppress inflammation. Treatment with TCS, is recommended to be used long term, a single of treatment is not sufficient.
  - Point out that the warning of side effects in the instruction leaflet of TCS may be ignored in the treatment of LS.
  - Half a fingertip of potent or ultrapotent TCS is sufficient, this must be applied to all sites that are affected by LS.
  - Daily use of greasy ointments, in particular in females, is necessary to protect the skin (as often as desired, but at least once a day). Explain about different types of emollients and let the patient find out what works best for her/him.
  - LS is a chronic disease which needs long-term treatment and follow-up.
- Self-examination of the anogenital skin. The patient needs to know what is healthy and what diseased skin, so tell the patient:
  - Regular inspection of their anogenital skin, if necessary by using a hand mirror or taking a photograph of the anogenital skin with a mobile phone, is necessary to observe any possible change. A physician should be seen in case suspicious changes are noticed (e.g., wounds that won't heal, thickened skin that doesn't resolve).
- Quality of Life (QoL). Anogenital LS may influence the QoL, affecting daily life like work, social activities, partnership or sexuality.[194,195] So inquire if patients experience any problems in daily life, ideally by introducing as follows:
  - 'We know from other patients and studies that LS can cause problems in (quality of) life. Are there things you would like to ask or discuss? E.g. changes in mood, sleeping problems, anxiety, depression, suicidal thoughts?'
  - 'Does your partner have any questions/concerns?'
  - 'Would you like more support, such as a referral to a psychologist or sexologist?'
  - Inform about national patient organizations, if available.
- Sexuality/ sexual health. Anogenital LS may influence sexuality because of the location of the disease in the anogenital site and the changes caused by LS. So inquire if patient experience any problems or have any questions concerning their sexuality and explain and inform as follows:

For females:

- Labia minora may become shorter, disappear and may fuse; the clitoral hood may cover the clitoris. These changes may lead to a narrowed introitus; in addition, the skin may become tight, and intercourse can become painful or impossible.
- Unaroused intercourse should (always) be avoided; sexual desire and arousal/lubrication and relaxation of the pelvic floor muscles is required.
- Lubricants—preferably hypoallergenic, for example, silicone based or petroleum based (white soft paraffin, Vaseline, glycerine)—and change of coitus position can help. Do not use emollients containing petroleum jelly in combination with condoms, because that reduces their reliability.
- Fused labia/clitoral hood over the clitoris do not directly cause problems reaching orgasm; but can reduce arousal due to fear and/or pain and result in problems reaching orgasm. A flat vibrator may be helpful for soft external stimulation to enhance vulval blood flow.
- A risk of ongoing painful intercourse can be sensitization/ hypersensitivity of the vulva and hypertonicity of the pelvic floor muscles.
- There is little evidence if stretching of the introitus (with fingers, dilators or penetrative sex) will harm and lead to worsening of LS (Koebner phenomenon) or if stretching will prevent narrowing of the introitus in the long-term.
- An alternative for painful coitus is non-coital sex. Inform that women (and their partner) can make the choice to give up intercourse; if feelings of guilt or shame hamper that decision, point at possibility of guidance by sexologist or medical psychologist.
- Surgical intervention is only applied if structures are fused and cause substantial problems. LS in females cannot be cured by surgery and recurrences are frequent!

For males:

- Friction of foreskin, glans and urethral opening can become painful during manual, oral and penetrative sex. Ejaculation can be irritating if the urethra is affected by LS. Lubricants and/or condoms can help. Lubricants/ emollients containing petroleum jelly in combination with condoms reduce their reliability.
- Urine is thought to be an important trigger in LS; therefore, men are advised to remove the last urine drop after urination carefully and possibly protect the skin with greasy emollients before and after urination.
- Surgical interventions, like circumcision, are recommended if topical treatment fails. This needs to be discussed with a specialized physician.
- Ask the patient: Do you want (more) support or a referral to a psychologist or sexologist? (You may have some colleagues you can refer to because it is often difficult to find such specialists.)

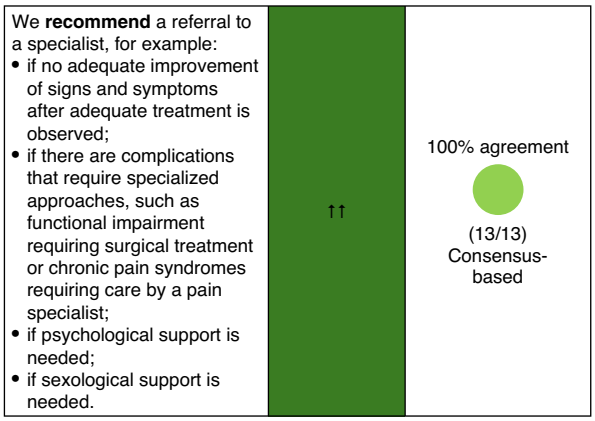
- Referral. Because of the impact of LS on quality of life and sexuality, the patient (and partner) should be informed

about the possibility of guidance/treatment and may be referred to a specialist like psychologist (in case of problems like shame, guilt, depression), sexologist (in case of sexual problems) or pelvic physiotherapist (in case of pelvic floor hypertonia).
- Patients need to have easy access to a list of physicians who are familiar with LS, and free contact information on the internet should be made available to all patients.

Lichen sclerosus patient organizations/Websites

Austria: www.lichensclerosus.at.
Denmark: www.lichensclerosus.dk.
France: www.lichensclereux.fr.
Germany: www.lichensclerosus-deutschland.de/home; www.verein-lichensclerosus.de.
Italy: www.lisclea.it.
Netherlands: www.lsnederland.nl/www.lichensclerosus.nl.
Switzerland: www.lichensclerosus.ch.
United Kingdom: www.lichensclerosus.org (no membership fee or annual meetings, only a website with information).

INTERDISCIPLINARY MANAGEMENT



When should patients be referred to another specialty or a physician specialized in LS?

LS affects the skin and anogenital mucosa in men and women, adults and children. Thus, LS occurs in a diverse population (men, women, adults and children) and has a huge impact on physical and psychological health because of the involvement of the anogenital site, the chronicity of the disease and complications that may occur.[182,196,197,198,199] The care of patients with LS is, therefore, shared between general physicians, paediatricians, dermatologists, gynaecologists, urologists, paediatric surgeons, psychologists, sexologists and physiotherapists. However, not each physician is equally familiar with LS in particular if complications occur. A multidisciplinary approach is mandatory in order to achieve adequate care and a referral is recommended:

- if a physician is not familiar with inflammatory anogenital diseases, for example, LS,
- if no adequate improvement of signs and symptoms after adequate treatment is observed,
- if there are complications that relate to other specialties, for example, patients, seen by dermatologists, who need specialized surgical intervention because of anal, meatal, urethral or introital strictures or patients seen by urologists who have not had adequate topical treatment for LS may be referred to a physician specialized in topical medical treatment (e.g., dermatologists/gynaecologists),
- if transition to adult medicine is necessary,
- if psychological and/or sexological support is needed.

Is there a need for interdisciplinary clinics?

Interdisciplinary clinics for the care, with an integrative approach, of patients with anogenital LS exist in several countries, for example, in the Netherlands, Denmark and the United Kingdom https://bssvd.org/.[200] This means that physicians of different specialties see the patient simultaneously during a consultation.

However, interdisciplinary clinics are costly and should therefore be reserved for special circumstances.

In favour of interdisciplinary clinics is a more comprehensive management, (a) giving the possibility to discuss potential options of care in case the disease is about to lead or already led to complications like strictures and cancer and (b) the possibility to provide a summarized, less conflicting information for patients. As a result, they may even be cost-saving if handled with care. We see the need for interdisciplinary clinics in the following situations to discuss the diagnosis, therapeutic approach and follow-up:

- if no adequate improvement occurs despite optimal treatment,
- to clarify special issues, for example, sexual abuse,
- if complications like strictures causing problems with urination or intercourse and
- if cancer development is an issue.

Ideally patients in these special situations are seen in an interdisciplinary clinic; however, if this is not possible due to local circumstances, an interdisciplinary referral needs to be arranged.

IMPROVEMENT OF CARE

We **recommend** raising awareness in the general population about lichen sclerosus.	↑↑	100% agreement (14/14) Consensus-based
We **recommend** raising awareness among health care professionals about lichen sclerosus.	↑↑	100% agreement (14/14) Consensus-based
We **recommend** that specialists document the signs and symptoms well, ideally taking a photo whenever required, and informing their colleagues to whom a referral is made of their findings.	↑↑	100% agreement (13/13) Consensus-based
We **recommend** that a list of physicians with experience in lichen sclerosus is made available to patients and referring doctors.	↑↑	>75% agreement (12/13) Consensus-based

Current situation

LS patients experience large differences in their care:

Some patients are seen at departments of Gynaecology or Dermatology at hospitals that may or may not be specialized in LS, others are seen by their gynaecologist or dermatologist, again who may be or not specialized in LS, and others are seen by their general practitioner.

However, many physicians do not know the disease or they do not have enough knowledge of the care of the disease. There is therefore a delay in making the diagnosis possibly leading to complications of LS (scarring/cancer development). This lack of knowledge also creates insecurity and anxiety in patients.

Access to physicians specialized in LS would help to diagnose the disease early and help the patient to better understand and treat their disease, this also improves compliance.

CONCLUSION 'AWARENESS & EDUCATION'

The general population needs to be educated about the existence of LS to recognize signs and symptoms early so LS can be treated as early as possible. Early treatment may prevent scar formation and cancer development.[61]

Physicians need to be educated about LS to recognize signs early and be able to initiate treatment as early as possible. In doubt, they need to refer patients to a specialist in LS.

Specialists should document signs and symptoms well, ideally take a photograph in the beginning, and inform colleagues about their findings (including a photograph) to guarantee support in care and educate.

Long waiting times for visits to specialists for LS could be bridged by educating general practitioners and local specialists.

A list of physicians specialized in LS should be made widely available to patients and referring physicians.

The ideal scenario is an interdisciplinary team or a LS centre with a team of specialists, including gynaecologists, dermatologists, urologists, physiotherapists, psychologists and sexologists, depending on the individual need of the patient, to provide individualized advice of care.

Need: Studies that evaluate the effect of care by specialists vs. non-specialists; the effect of interdisciplinary clinics on care and economic implications.

Interdisciplinary team: gynaecology, dermatology, urology, paediatric surgeon, specialized pathologist/dermatopathologist, general practitioner, psychologist/sexologist, pelvic floor therapist.

FUTURE RESEARCH

In a James Lind Alliance Priority Setting Partnership, physicians and patient representatives determined the 'Top 10 uncertainties' to be addressed in future research.[201] The list below is based on identified uncertainties and is complemented by additional important research questions.

Important research questions:

Diagnosis

- What is the best way to diagnose LS?
- On what criteria should the diagnosis be based upon?

Pathophysiology

- What is the precise pathomechanism in LS?
- Is LS an autoimmune disease?[202,203]
- Developments of in vivo and in vitro models of LS (such as already available for psoriasis[204] or atopic dermatitis[205]) are needed for translational research.
  - Such models could be crucial to deepen the understanding of the disease mechanisms in LS and to identify novel therapeutic targets.
- What are the pathophysiological similarities and differences between LS and lichen planus?
  - Why do some patients have an overlap between LS and lichen planus?
  - Does overlap between LS and LP exist or has an individual patient only one disease, how to define overlap between LS and LP?
  - Will anti-inflammatory treatments investigated for lichen planus (e.g., apremilast, JAK inhibitors or

anti-IL-17 antibodies) and morphoea (clinical trial using Dupilumab) be candidates for the treatment of LS?

Risk factors

- What are potential risk factors or triggers for LS?[22] (see also chapter trigger factors)
  - Can their avoidance prevent the development or progression of the disease?
  - Is there a link between microbiota and LS?[206]

Genetics

- Genetic sequencing studies are needed to determine if there is a genetic link

Gender and age differences

- Is the pathomechanism of LS the same in men and women, children and adults?
- Can treatment recommendations be adopted from one sex to another and from adults to children?[207,208]

Cancer

- Why is LS associated with an increased risk of genital cancer?
  - How to detect LS patients with increased cancer risk?
    - What are predisposing factors for the development of genital carcinomas in LS patients?
    - Are there reliable early clinical indicators that suggest the development of cancer in LS patients?
    - Are there early features, for example, histopathological and detectable precursor markers (e.g., p53 and Ki-67) for malignant transformation?[209,210]
  - How can the risk of genital cancer development be decreased in genital LS?
  - Can adequate therapy reduce the risk of cancer development in LS patients?[61]

Course of LS

- How to avoid anatomical changes, which often lead to a poor sexual life and have an high impact on quality of life
- Are there distinct patters of LS or is there only one 'LS'? for example, are hypertrophic variants, genital/extragenital LS/scarring/non-scarring LS all the same disease?
- How often does LS in children (boys and girls) persist in adulthood?
- Should all children with LS be followed up in adulthood and for how long?
- Does it make sense to stage LS and is there a histological and clinical correlation of the changes?[211] Or is it better to just describe the clinical changes and their progression in a defined and systematic manner, as outlined in Kirtschig & Cooper p.26, Figure 5.1.[12] and Meuli 1994 describing the progression of penile changes.[83]

Treatment

- More randomized controlled trials are needed to determine if new treatment options are effective and in whom. This concerns in particular the following treatment options:
  - Oral Doxycycline (see chapter trigger factors and chapter future research in the second part of the guideline)
  - Adipose tissue stromal vascular fraction[212]
  - Energy-based modalities such as the fractional CO2 laser treatment (see chapter treatment in the second part of the guideline)
  - Treatment with Polydeoxyribonucleotide[213]
  - Platelet-rich plasma[214] (see also chapter treatment in the second part of the guideline)
  - Photodynamic therapy (see chapter treatment in the second part of the guideline)
  - High intensity focused ultrasound
  - Hyaluronic acid applications/combined with oxygen.[215]
  - Biologics (e.g., TNF alpha inhibitors) and small molecules (e.g., Apremilast (Phosphodiesterase-4-Inhibitor), Janus kinase inhibitors, topical JAK inhibitors, Dupilumab anti-IL-4/ IL-13, Tralokinumab anti-IL-13, Nemolizumab IL-31RA, Rituximab anti-CD 20, anti-IL-17 and anti-IL-31) which might possibly interfere with the pathophysiology of LS (see chapter upcoming treatments in the second part of the guideline)
- Cold atmospheric pressure plasma.[216,217] Are there key mediators that could potentially be targeted therapeutically?[203]
- When, in whom and what surgical treatments should be offered for LS?
- Is it necessary to continue treatment for patients with LS who do not have any symptoms and/or signs of disease activity? A randomized controlled trial is underway that addresses this question https://www.fundingawards.nihr.ac.uk/award/NIHR135121
- MC2 Therapeutics has patented and initiated development of drug candidates for chronic kidney disease associated pruritus (Stages 3–5) and LS. The pathogenesis of genital LS is possibly driven by chronic urine exposure leading to nerve changes and skin damage caused by carbamylation. A leading drug candidate is an effective isocyanate scavenger demonstrating >90% inhibition of protein carbamylation and counteracting the morphological skin changes induced by carbamylation. This may offer new treatment approaches. https://www.prnewswire.com/news-releases/mc2-therapeutics-announces-breakthrough-discovery-with-the-potential-to-help-millions-of-people-suffering-from-urea-associated-skin-diseases-301615674.html?tc=eml_cleartime.
- What role does complementary therapy play in LS? Many forms of alternative medicine are offered to patients;

however, they are usually not well investigated and must not replace gold standard treatment. Aromatherapy, using, for example, essential oils and other aroma compounds, is such an attempt; however, there are no studies available that support its benefit in the treatment of LS. Well-designed studies are needed.

Core outcome set

- There is a lack of standardized, mandatory outcomes that are recorded by all clinical trials, and therefore, trial results are not comparable in meta-analyses. The development of a core outcome set (COS) has been initiated.[201] Outcomes consist of 'domains' (what to measure) and 'instruments' (how to measure). Consensus was met in 2022 for the domains 'quality of life – LS specific', 'symptoms' and 'clinical (visible) signs', and *this* needs to be further developed.[218]
- www.nottingham.ac.uk/go/CORALS

Patient care

- When do we need an interdisciplinary approach in the care of LS? (see also chapter improvement of care)
- How to organize the transition of affected children to adult medicine after puberty?[208]
- How to reduce the diagnostic delay in LS?[219]
- Awareness: How to best inform patients, clinicians and nursing staff about LS?

STRENGTHS AND LIMITATIONS

The vision of this guideline was to provide a comprehensive evidence-based update on all aspects of LS care with high relevance to the practising clinicians.

The formal structure of the guideline document has been changed to follow the structure and style of the EuroGuiDerm guidelines, and this reflects the latest methodological rigour in guideline development.

We assembled a guideline development group (GDG) that included clinical and methodological experts from across Europe, including patients. Our clear conflict of interest policy has created more transparency.

The biggest drawback of this guideline is the lack of randomized controlled trials performed in LS. Topical corticosteroids remain the gold standard; however, in recent years, interest in LS increased and new treatment approaches are in development, and this may mean that this guideline will soon be outdated.

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CONFLICT OF INTEREST STATEMENT

This is a brief summary of the update of the EuroGuiDerm Guideline on Lichen sclerosus. For the complete guideline, methods report (including COI disclosures) and evidence report see https://www.guidelines.edf.one/edf-guidelines-and-consensus-statements, the evidence and methods reports are also provided as Appendix S1 to this publication.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

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SUPPORTING INFORMATION

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

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