

SPECIAL ARTICLE

Diagnosis and management of cutaneous and anogenital lichen sclerosus: recommendations from the Italian Society of Dermatology (SIdMaST)

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ABSTRACT

Lichen sclerosus (LS) is a disabling chronic inflammatory disease of skin and genital mucous membrane causing itch, pain, dysuria and restriction of micturition, and significant sexual dysfunction and dyspareunia both in women and men. If left untreated, LS is associated with a high degree of sclerosis and scarring, as well as with an elevated risk of cancer in the genital area. Although a central role of autoimmunity is suggested, the pathogenesis of LS is still not clearly understood and the disease remains difficult to treat. The goals of treatment of LS are to alleviate symptoms and discomfort, prevent anatomical changes and prevent malignant transformation. This guideline has been developed by an Italian group of experts. It summarizes evidence-based and expert-based recommendations. The highest level of evidence favors the use of topical high potency corticosteroids; second- and third-line treatments include topical calcineurin inhibitors and topical retinoids, respectively. Surgical treatment has become the treatment of choice in male genital LS with persistent phimosis not responsive to medical treatment. The aim of this paper is to offer evidence-based and easily applicable recommendations for the management of LS.

(Cite this article as: Papini M, Russo A, Simonetti O, Borghi A, Corazza M, Piaserico S, *et al.*; Mucous Membrane Disorders Research Group of SIdMaST. Diagnosis and management of cutaneous and anogenital lichen sclerosus: recommendations from the Italian Society of Dermatology (SIdMaST). Ital J Dermatol Venereol 2021;156:519-33. DOI: 10.23736/S2784-8671.21.06764-X)

KEY WORDS: Lichen sclerosus et atrophicus; Vulvar lichen sclerosus; Rare diseases; Guideline; Drug therapy; Operative surgical procedures.

Introduction

Lichen sclerosus (LS) is a chronic inflammatory disease of skin and genital mucous membrane causing itch, pain, dysuria and several other disabling sexual effects.¹ LS is associated with a high degree of sclerosis and scarring and possible cancer transformation.² The pathogenesis of LS is still not clearly even if an autoimmune mechanism has been demonstrated.³

Sexual and urinary dysfunction are the main manifestations of genital LS in male patients, while itch is the dominant symptom in females.^{1, 4} Advanced scarring disease severely affects the quality of life by interfering with function (particularly sexual function) and self-image and is associated with an increased risk of squamous cell carcinoma (SCC). Early diagnosis, prompt treatment and long-term follow-up of affected patients are mandatory.⁴ 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 about the different therapeutic options and their advantages and disadvantages explained enabling them to make a decision. The guideline summarizes recommendations based on evidences published on medical literature or expressed by an expert consensus.

Methods

The present guideline has been developed by the “Mucous Membrane Disorders” research group of the Italian Society of Dermatology SIDEmaST on the basis of available evidence, as well as consensus of experts with a well-recognized experience, taking in account the Italian legislation and local pharmacological governance.

1. Assessment

1.1 Goals

- 1) Diagnostic pathway.
- 2) How to undertake a comprehensive history, including psychosexual issues and urinary symptoms.
- 3) Possible association with autoimmune diseases.
- 4) Evaluation of the age-dependent prognosis.
- 5) Therapeutic options.

1.2 Clinical features

A comprehensive medical history and a full physical examination of the anogenital area should be done, looking for signs and symptoms of LS. LS lesions are flat, ivory-colored spots, which tend to coalesce into crinkly patches and plaques. Erythema may be adjacent to these pale lesions. Ecchymosis and itching-related excoriations are common, while hyperkeratosis may be occasionally present. Purpura or ecchymoses are late onset harmless lesions, but sometimes they are the clinical pictures detected at the first dermatological examination. Moreover, the Koebner phenomenon is frequent.¹

Cutaneous LS is rare and mostly affects women.⁴ The classical sites are the upper trunk, axillae, buttocks and lateral thighs. It is generally thought that LS does not affect the oral mucosa, nails or vagina; however, the occurrence at these sites has been reported.⁵

LS in women usually involves labia minora and majora, clitoris and clitoral hood, perineum and perianal area, sometimes giving rise to the evocative “figure-of-eight” shape. Scarring is common and is observed in about 80% of women and 30% of girls with LS.² It may lead to loss

and agglutination of the labia minora, possibly midline fusion with sealing of the clitoral hood and burying of the clitoris. Women show a wider panel of symptoms in comparison to males, including local itching and burning and often pain during intercourse. The sexual dysfunction is often important in women and sometimes may be greater than in male patients, leading to intense dyspareunia and sexual avoidance. The involvement of perineal, anal and perianal areas can lead to bleeding and painful defecation and sometimes anal stenosis.³

LS in adult and adolescent males usually occurs on the glans penis and/or foreskin, with a predilection in the peri-frenular area, and may cause phimosis in previously retractable foreskin or adhesions of the foreskin to the glans, causing dysuria and painful erection. In males, the meatus is more often involved with possible obstruction and stenosis. Subjects who were circumcised for religious reasons, rarely develop LS.^{6, 7}

1.3 Counselling

The typical LS patient is a woman of roughly 50 years of age with external genital itch. The urge to scratch is very strong. When asked explicitly, pain during sexual intercourse is often reported. Itching is a minor problem in males, while the predominant symptom may be painful erection due to acquired phimosis. LS is less frequent in children. Girls typically suffer from anogenital itching and possibly from constipation and painful defecation. Boys complain of a narrowing of the foreskin, possibly accompanied by sclerosis. This phenomenon has to be differentiated from the physiological phimosis that generally regresses by puberty.⁴

1.4 Diagnosis

The diagnosis of LS is usually clinical, and histological examination is not always mandatory. This is particularly true in children. Dermoscopy may be included as a part of the clinical inspection of anogenital areas to support non-invasive LS diagnosis and choose the optimal biopsy site in order to minimize sampling error.^{8, 9}

Patients will need a biopsy if:

- there are atypical clinical features;
- there is a suspicion of neoplastic change, *i.e.* a persistent area of thickened scaling skin, persistent erosion or erythema, or warty or papular/nodular lesions;
- the first-line recommended treatment fails to control the symptoms and progression of the disease;
- there are pigmented areas, in order to exclude abnormal melanocytic proliferation.

Typical histological features of LS are orthohyperkera-

TABLE I.—*Diagnostic criteria of lichen sclerosis.*

Diagnostic criteria of lichen sclerosis	
Anamnestic data and symptoms	• Anogenital LS in female: itch (primarily in the anogenital area), pain/sensation of soreness, fragility of the skin, dyspareunia/apareunia • Anogenital LS in male: recurrent balanitis, phimosis, glans hypoesthesia, impeded urinary flow • Constipation (often in children) • Cutaneous LS: rarely symptomatic, itch
Clinical aspects	• Anogenital LS in female: pale, ivory-colored lesions, partially atrophic skin; “figure-of-eight” distribution around vulva and anus; purpura/ecchymosis (localized hemorrhage of the skin); hyperkeratosis (whitish, thickened lesions); sclerosis; fissures, erosions/ulcerations; varying degree of scarring • Anogenital LS in male: pale, ivory-colored lesions of the glans and foreskin; purpura/ecchymosis; fissures, erosions/ulcerations; progressive phimosis and urethral/meatal stenosis; non retractile foreskin and painful erections; dysuria • Cutaneous LS: pale, ivory-colored papules, that coalesce into plaques; progressive atrophy with crinkling or cellophane paper-type appearance; follicular plugging • Most common locations: buttocks, thighs, breasts, submammary area, neck, back and chest, axillae and wrists
Histopathology	Not mandatory, except in the following cases: • Atypical clinical aspects • Suspicion of neoplastic changes • Treatment failure with progression of disease

toxis, epidermal atrophy, basal cell degeneration, dermal hyalinization, and a band-like lymphocytic infiltrate.¹⁰ However, in early LS some features like the hyalinization of the upper dermis may be lacking and a firm diagnosis cannot be made. Also, mucosal/erosive vulvar lichen planus may show similar clinical and histological features making a distinction between the two diseases impossible in some cases. Histopathology should not be performed in a very early stage since dermal hyalinization is not present.¹¹ The site of the biopsy is important and skin specimen should be taken from the most active sclerotic area.

Diagnostic criteria are summarized in Table I.

2. Epidemiology

2.1 Incidence/prevalence

The incidence of LS is not exactly known and probably underestimated as it is either asymptomatic or under-recognized, ranging between 0.1% (child) and 3% (postmenopausal female).^{1, 12} Women are more affected than men with a F:M ratio variable between 3:1 to 10:1, while a positive family history has been reported in about 10% of females (much less in males).^{1, 13, 14} Lower estrogen levels are associated to the two peaks of disease incidence in women, before puberty and postmenopausal period, whereas in men LS is onset after puberty and after 60 years.^{1, 3, 13, 15}

3. Etiology and pathogenesis

The cause of LS is still not fully understood and several factors should be taken into account.

3.1 Genetics

A genetic predisposition is implicated in disease development. A twofold higher incidence of LS has been described in the United States among the Black and Hispanic male patients in comparison to the white.¹⁵ A positive family history has been reported in 12% and 8.7% of patients with vulvar LS, whereas there is a little evidence of familial predisposition in boys.^{13, 16} Some studies have demonstrated that HLA class II antigen DQ7 and DRB1*12 (DR12) and haplotype DRB1*12/DQB1*0301/04/09/010 are significant associated with LS,¹⁷ while DRB1*0301/04 (DR17) and haplotype DRB1*03/DQB1*02DRB1*0301/DQB1*0201/02/03 have a lower frequency.¹⁸ Most of these regions are implicated in autoimmune diseases predisposition. Enzymatic epigenetic alterations are also possible promoters of the disease.¹⁹

3.2 Immunology

An autoimmune phenotype has been observed in the case of vulvar LS involving increased levels of Th1-specific cytokines, thick T cell infiltrate and enhanced BIC/miR-155 expression.²⁰

A distinct expression patterns of tissue remodeling-associated genes [bone morphogenetic protein 2 and its corresponding receptor, matrix metalloproteinases (MMP) 1 and 9, tissue inhibitor of MMP 1, cytokine chemokine ligands 5 (also known as RANTES, meaning Regulated Upon Activation Normal T cell Express Sequence), interleukin 4, transforming growth factor- β and its corresponding receptor] was observed in boys with congenital phimosis and LS.²¹

The lower CD44 expression by keratinocytes and hyaluronate accumulation in upper dermis can contribute to skin damage.²²

Circulating IgG autoantibodies targeting extracellular matrix 1 protein (ECM1) have been demonstrated in sera of 74% women with anogenital LS compared with 7% of controls. ECM1 auto reactivity was more likely in patients with disease duration greater than 1 year and/or more extensive disease. Authors suggest that ECM1 autoimmunity might be involved in progression rather than in initiation of the disease.^{23, 24} Antibodies targeting the basement membrane zone (bullous pemphigoid [BP] 180 and BP230) have been found in 30-40% patients with vulvar LS.^{25, 26} However, these autoantibodies seem to represent an epiphenomenon rather than a true component of LS pathogenesis. Oxidative stress to lipids, DNA and proteins may contribute to sclerosis, autoimmunity and carcinogenesis in LS.²⁷

3.3 Disease associations

As several other autoimmune disorders, LS is associated, more in women than men, to other autoimmune diseases such as vitiligo, alopecia areata, inflammatory bowel diseases, rheumatoid arthritis, primary biliary cirrhosis, pernicious anemia, localized scleroderma/morphea, systemic lupus erythematosus, and multiple sclerosis.²⁷⁻³² In a recent Italian study, overweight and obesity, as well as blood hypertension, resulted more frequent among the LS patients than in the general population.³³

3.4 Trauma

It is assumed that trauma (Köebner phenomenon) and several urine chemicals play a significant role as trigger in the development of LS. Any kind of trauma including friction, surgery, invasive treatments and even delivery may be a trigger.³⁴⁻³⁹

LS rarely occurs in boys circumcised at birth and this may support the concept that a moist environment under the foreskin predisposes to LS.⁴⁰⁻⁴³ Circumcision removes the occlusive effect of the foreskin and reduces the onset of the Köebner phenomenon and consequences of micro-incontinence after micturition.⁷

3.5 Hormonal factors

In case-control studies free serum testosterone and androstenedione were significantly decreased in patients with untreated vulvar LS. At menarche, there is increased metabolism of testosterone in genital skin which may re-

sponsible for the spontaneous improvement in childhood vulvar LS. These results seemed to suggest that decreased 5 alpha-reductase activity was an aetiologic factor for LS.⁴⁴ Even lower density of androgen receptors have been associated to LS progression.⁴⁵ Based on those findings, treatment with topical testosterone was used in the past, but it has been abandoned due to the lack of evidence of effectiveness and androgenic side effects. The use of oral contraceptives, especially those with anti-androgenic properties, was found to trigger the early onset of LS in a subgroup of susceptible young women.⁴⁶

3.6 Infections

Weak evidence supports a role of *Borrelia*, papillomavirus and other infections.⁴⁷⁻⁵⁰

3.7 Drugs

Rare reports associate LS with oral imatinib mesylate and carbamazepine. In addition, an inverse relationship between the presence of vulvar LS and the use of beta-blockers (blocking cyclic AMP levels) and ACE inhibitors was described.⁵¹⁻⁵³

3.8 Triggers and cofactors

Over the years, several potential trigger factors (oral contraceptives with antiandrogenic properties,⁴⁶ family history of diabetes mellitus,¹³ previous pelvic surgery,¹³ and maneuvers of mechanical reduction of the foreskin performed at least 5-10 times per month)³⁸ or protective factor (use of barrier methods for contraception, progestin-only contraceptive, and hormone replacement therapy)¹³ have been reported in association with LS. To date, only accidental or surgical wounds, radiotherapy and sunburns should be considered as relevant factors in LS pathogenesis.⁵⁴

4. Complications

4.1 Malignancy

Squamous cell carcinoma (SCC) has been described in association with both female and male genital LS.⁵⁵ The estimated lifetime risk to develop SCC is approximately 4-5% in both sexes,^{56, 57} although in men some authors reported a risk ranging from 0% to 12.5%.⁵⁸⁻⁶⁰

The role of human papillomavirus (HPV) in LS-associated SCC is debated. HPV may be found in intraepithelial neoplasia associated with LS in both sexes.⁶¹⁻⁶³ However, Paolino *et al.* suggested that HPV is not identifiable in most cases of LS associated malignancy and when it is

detected it may be a non-oncogenic type.⁶⁴ LS may act both as initiator and promoter of carcinogenesis without any HPV correlation.

4.2 Scarring

In female genital LS, anterior and/or posterior fusion of the labia can lead to a tightening of the introitus. It can cause, along with skin fragility and tissue elasticity loss, relevant dyspareunia and difficulty of micturition.^{65, 66} Occasionally, clitoral hood adhesions seal over the clitoris and keratinous debris builds up underneath forming a painful pseudocyst.⁶⁷

In male genital LS, the frenulum often becomes contracted due to scarring and circumferential involvement of the preputial aperture leads to a progressive fibrous phimosis. Adhesions may be trans-coronal or sub-coronal and they may require surgical reduction usually during circumcision. Urethral involvement is reported to occur in 20% of males affected by LS. It may start at the meatus and may spread proximally to involve the penile and bulbar urethra.⁶⁸

4.3 Sensory abnormalities

Some affected patients have persistent itch and pain. They may suffer from vulvar or penile dysesthesia despite successful control of the inflammation and objective clinical improvement or resolution of skin lesions.

4.4 Social/sexual problems

Patients suffer from embarrassment when they have to speak about the disease or the need to satisfy the insatiable itch. Their social activities are limited, since their clothing must be suitably selected (not too tight) and some sports (horseback riding, bicycling) are only feasible to a limited extent because they strain the genital area too much. Dyspareunia, apareunia and difficulty in achieving orgasm will affect sexual life of men and women. The symptoms may relate to continuing inflammatory disease as well as to anatomic changes and scarring from long-standing active disease.^{68, 69}

5. Course of disease and prognosis

5.1 Course of the disease with or without treatment

In male and female patients, LS is usually a scarring, chronic progressive or relapsing remitting, lifelong condition. The number of spontaneous remissions, in particular in early and mild cases, is unknown as these individuals

may not present to a physician. Treatment is reported to relieve symptoms such as itching and pain in 80% to 90% of female patients.² However, complete clearance of symptoms and signs seems an unrealistic treatment goal with a conventional 12-week duration therapy.⁷⁰ Scarring is irreversible and it is not known if early treatment will prevent it. At least in males, potent topical corticosteroids and early circumcision seem effective and allow a complete or good improvement.⁵ In female subjects the disease control is more difficult than male and at least a 75% of patients do not achieve remission. 75% of girls who develop LS prior to puberty will continue to require maintenance therapy after menarche.⁷¹⁻⁷³ A cohort study on vulvar LS indicates that early and long-term treatment decreases scarring by 36.6% and the development of carcinoma by 4.7% after an observation period of 4.7 years.⁶⁵ However, conclusive evidence is still lacking.

5.2 Course during pregnancy

LS usually improves during pregnancy and the amelioration has been related to a protective role of estrogens. It should be emphasized that, according to disease stage and clinical symptoms, topical steroids or calcineurin inhibitors may be safely used during pregnancy and puerperium, if needed.

Vaginal delivery is not contraindicated if vulvar changes and sclerosis degree may allow it. Anyway, the preferred mode of delivery should be discussed with the patient and her obstetrician.⁷⁴

5.3 Follow-up

Patients with LS should be managed by dermatologists experienced in treating the condition with the help of a multidisciplinary team including general practitioners, urologists for adult male with phimosis or urethral stricture, andrologists, gynecologists for adult women with LS not responding to medical therapy, pediatricians and pediatric surgeons, sexual health physicians.

LS has a relevant impact on quality of life. Genital LS is particularly impacting on sexual function. Psychosexual issues are common in both men and women and may persist also after successful treatment.⁷¹ For these reasons, it is important to offer the patient a referral to expertise of these problems and a psychological support.⁷⁵

6. Therapy

All genital LS cases should be treated, even if asymptomatic, with the goal of preventing scarring and its associated

disfigurement, sexual and urinary dysfunction, and reduction in quality of life. Treatment effect is typically evaluated every 3 months when topical drugs are used. Efficacy is gaged by the improvement of symptoms (pruritus and pain) and clinical manifestations, *e.g.* ulceration, hyperkeratosis, erythema, ecchymosis, atrophy, and depigmentation. Repeated clinical pictures are helpful for monitoring from visit to visit.

There is not a single optimal therapeutic strategy for the management of LS.

Multiple randomized controlled trials (RCTs) evaluated different topical interventions, while two assessed the use of oral acitretin, and one of oral para-aminobenzoate. The efficacy data for other agents include small studies and case reports.

The first-line treatment is the application of an ointment containing potent or ultra-potent corticosteroid like clobetasol propionate (CP) 0.05%. A safe and effective treatment option suggests to apply the ointment for 3 months, once or twice per day, tapering the number of applications after one month. The same treatment regimen can be applied to children. Thinning of skin could appear after 2 weeks of therapy but resolve after the treatment cycle. An equally effective alternative is the off-label use of topical calcineurin inhibitors such as tacrolimus and pimecrolimus.⁷⁶⁻⁷⁸

Topical retinoids may represent a useful alternative option to corticosteroids, even if local adverse effects occur in about a third of treated patients.⁷⁹ No significant benefit for topical testosterone, dihydrotestosterone and progesterone is demonstrated in RCT.

Clearance of LS after circumcision in males with mild to intermediate disease is described in the majority of cases (the cure rate is nearly 100%).⁸⁰⁻⁸² However, there are no randomized controlled trials confirming this, and good long-term follow-up studies are lacking. If the initial three-month treatment with topical drugs does not lead to the complete recovery in male LS patients, a complete circumcision should be recommended, especially in uncomplicated cases at early stages.⁴

In treatment of resistant LS several options may be tried and are dependent on sex, age and other individual circumstances: steroid injections and/or oral retinoids, cyclosporine, methotrexate and fumarates. In addition to pharmacological therapy, application of emollient creams several times per day (after contact with water or urine) should be recommended. General measures like the avoidance of mechanical irritation (*e.g.* by using rough paper towels, moistened toilet tissues or hard bicycle saddles) and use of silk underwear can alleviate discomfort. Special intimate

care products are not necessary in the ongoing management of genital LS.

Table II and III summarize medical and surgical treatments of genital LS.

6.1 Topical treatment

Topical glucocorticosteroids (Evidence level: 1 to 2; Recommendation grade: A).

Topical application of CP 0.05% ointment (or cream) is the gold standard treatment for vulvar LS in women and girls.⁸³ The original study by Dalziel *et al.*,⁸⁴ which demonstrated the efficacy of topical CP ointment 0.05% in inducing remission in vulvar LS (VLS), has been validated by other authors. Usually a fingertip per application and a maximum amount of 10 g per month (possibly a little more for initial treatment) is recommended to avoid skin atrophy.

- The most valuable studies on topical steroids are summarized as follows:⁸⁵⁻⁹¹

- CP vs. placebo 3 months period in female: 75% of patients showed improvement with no adverse events;

- CP vs. mometasone furoate (MF) in 54 women: at 12 weeks both treatments were effective and safe in 88.9% of patients;

- CP in prepubertal treatment was safe and effective in a 3 month-period achieving about 70% success;

- CP in 22 men after 7 weeks show 70% improvement clinically and histologically. Similar results were seen in 40 young boys in other 2 studies. Most of the studies demonstrated that early lesions respond better than late lesions.

Corticosteroid formulations seem to influence treatment outcome in vulvar LS. In particular, MF in ointment formulation has been found to be more effective in treating active vulvar LS, especially in improving symptoms, in comparison with MF cream.⁸⁹ A long-term follow-up of childhood LS in 15 girls with a mean follow-up of 4.7 years showed the best therapeutic response with an early aggressive treatment, a high recurrence rate of 60% after 1 year from the first cleaning and the need for maintenance therapy.⁹²

The most recent case series indicates that treatment with topical CP (for about 12 weeks with decreasing frequency) is successful in 60% of 185 men affected by LS. Patients who failed topical steroid treatment were subsequently circumcised.⁷

Steroid maintenance treatment

Topical steroids are safe and effective even in a long-term maintenance treatment of LS. It is reported that such ef-

TABLE II.—*Summary of medical treatment for genital lichen sclerosis.*

Recommended regimen	Dosage	When to choose	When to stop
First-line Topical ultrapotent or potent steroids (e.g. clobetasol propionate 0.05% or mometasone furoate 0.1% in ointment)	- Once daily for the 1st month, then on alternate days for the 2nd month and twice weekly for the 3rd month OR - Once daily for 1-3 months (preferred in men) - Maintenance therapy with once or twice medications per week	Symptomatic or asymptomatic LS, with the goal of improve/preventing inflammation/scarring and get better quality of life	- Clinical remission - Severe side effects or adverse reactions - Treatment failure → consider a second line treatment or surgical options - Worsening of symptoms or disease progression → clinical re-evaluation; consider biopsy for possible neoplastic changes
Intralesional steroid injections (triamcinolone acetonide or dexamethasone solution)	- Monthly intra/subdermal steroid injection for 3-4 months - Maintenance treatment required	Patients unable to apply topical steroids (because of particular locations or physical limitations)	
Second-line Topical calcineurin inhibitors (e.g. tacrolimus 0.1% ointment or pimecrolimus 1% cream)	Once or twice daily for 4-8 weeks	First line treatment failure or intolerance to topical steroids	- Clinical remission - Severe side effects or adverse reactions - Treatment failure → consider a third line treatment or surgical options - Worsening of symptoms or disease progression → clinical re-evaluation; consider biopsy for possible neoplastic changes
Third-line Topical retinoids (e.g. tretinoin 0.025% cream)	On alternate days for 12-24 weeks	- Previous treatment failure - Hyperkeratotic lesions	- Clinical remission - Severe side effects or adverse reactions - Treatment failure → consider alternative treatment or surgical options - Worsening of symptoms or disease progression → clinical re-evaluation; consider biopsy for possible neoplastic changes

TABLE III.—*Surgical treatments for genital lichen sclerosis.*

Lichen sclerosis	Surgical procedure	Indications
Male lichen sclerosis	- Circumcision - Meatal dilatation - Meatotomy/meatoplasty - Urethroplasty/urethral reconstruction with oral mucosal graft	- Persistent phimosis not responsive to medical treatment - Tight or irreducible phimosis - Meatal stenosis - Urethral stenosis
Female lichen sclerosis	- Dissection or debridement of the small labia - Circumcision - Perineotomy and reconstruction - Vulvectomy - Urethroplasty	- Fusion of the labia minora - Clitoris pseudocysts - Introitus stenosis - Reserved for cases with vulvar malignancy or severe dysfunctional anatomical changes - Urethral stenosis

fectiveness is greater in females than males. Once the disease and symptoms suppression have been achieved, long-term management should be initiated aiming to prevent recurrence and neoplastic evolution. The current evidence

shows a statistically significant improvement in disease outcomes in patients who used preventive treatment regularly, even if they are asymptomatic.

Once VLS has been stabilized with topical corticoste-

roids, twice-weekly proactive application of MF 0.1% ointment over 52 weeks was found to be an effective and safe therapy option in maintaining VLS remission and in preventing the occurrence of relapse.⁸⁷ In a group of 25 patients with vulvar LS, who achieved disease remission after 12-week treatment with topical MF 0.1%, 10 patients (40%) experienced a relapse by the end of maintenance phase: five in the vitamin E group (56%) and five in the cold cream group (62%), while no patient in the MF.⁹³ Similar results in efficacy and safety are reported in other two retrospective studies.^{2, 94}

A recent prospective longitudinal cohort study on 507 women with biopsy proven vulvar LS continuously treated with topical corticosteroids and followed up for a minimum of 2 years (mean follow-up 4.7 years) showed that this treatment strategy led to return skin to normal appearance in the majority of cases. The authors also demonstrated that no SCC or vulvar intraepithelial neoplasia occurred during follow-up in treatment compliant patients vs. 4.7% of partially compliant patients.⁶⁵

In order to minimize corticosteroid exposure, it is the successful practice of many clinics to lower the frequency, rather than potency of applied corticosteroids once remission has occurred and maintenance therapy is required.

GLUCOCORTICOSTEROIDS INJECTIONS (EVIDENCE LEVEL: 1+; RECOMMENDATION GRADE: B)

In selected patients with resistance to topical steroids or unable to use them the local injection of corticosteroids can be a valuable alternative. The most relevant long-term study recruited 88 patients with histologically proven LS. The injections were given each month until the patients were free from pruritus and demonstrated no progression of clinical manifestations.⁹⁵

Other studies confirmed the efficacy of intralesional triamcinolone acetonide in decreasing severity scores both for symptoms and physical findings.^{96, 97}

TOPICAL SEX HORMONES (EVIDENCE LEVEL: 1+; NO RECOMMENDATION GRADE A)

In postmenopausal women topical oestrogens have been suggested in combination with topical corticosteroids (lack of evidence as monotherapy). A 2% progesterone cream resulted not effective, whereas a positive outcome was achieved with an 8% concentration.⁹⁸ Topical applications of testosterone and dihydrotestosterone proved ineffective and also a worsening of the disease was reported.

Two RCTs did not find significant efficacy of testosterone 2% vs. placebo after application for 3 months and 1

year, respectively.^{44, 99} One RCT found that after 3 months' application, testosterone 2% was significantly less effective than CP.⁸⁵

A very small crossover trial randomized five participants to receive either dihydrotestosterone or placebo for 3 months. No women showed an improvement of their symptoms with either preparation.¹⁰⁰

A small study reported that the sequential use of topical testosterone for 24 weeks was not effective to maintain the improvement of symptoms and signs of vulvar LS that was obtained with an initial 24-week treatment with CP 0.05% cream. No significant differences in adverse drug reactions between testosterone and placebo were found.¹⁰¹

Topical calcineurin inhibitors

TACROLIMUS (EVIDENCE LEVEL: 2+; RECOMMENDATION GRADE: C)

A multicenter, phase II trial evaluated the safety and efficacy of tacrolimus ointment 0.1% for the treatment of LS.⁷⁷ In 84 subjects of both sexes complete remission was achieved in 43% and partial remission in 34% of patients. Burning and itching were reported in the first days of treatment, leading two patients to intermittently stop tacrolimus application and one patient to withdraw from study. In two studies of 12 and 8 week-duration respectively, tacrolimus 0.1% ointment led to complete remission in almost all treated cases.^{102, 103} A double-blind RCT showed that topical CP 0.05% ointment was significantly more effective in treating signs and symptoms of vulvar LS than topical tacrolimus 0.1% ointment.¹⁰⁴

One study tested the effects of tacrolimus 0.1% or methylprednisolone acetonide 0.1% as maintenance therapy, suggesting that there is no difference between the two in preventing the relapses.¹⁰⁵

Treatment of extragenital LS with tacrolimus combined with UV light was used successfully in few patients.^{106, 107}

In children topical tacrolimus 0.03% appears to be safe and effective also as a long-term maintenance therapy twice a week.¹⁰⁸

PIMECROLIMUS (EVIDENCE LEVEL: 1+; RECOMMENDATION GRADE: B)

A RCT enrolled 38 women with biopsy-proven LS: 17 women in the pimecrolimus group (twice daily) and 19 women in the clobetasol group (once daily) for 12 weeks. Although there was no statistically significant difference in subjective improvement of pruritus, burning and pain or objective assessment by investigator between the two treatment groups, clobetasol was reported to be more effective in improving inflammation.⁷⁸

The relief of symptoms in LS by pimecrolimus is also supported by several case series.^{109, 110}

There are few reports of the treatment of LS with pimecrolimus in children. Treatment of vulvar LS in children/girls with pimecrolimus was effective in a few studies and therefore it may be considered an alternative to topical steroids.^{111, 112}

There are controversial opinions about the long-term safety of topical calcineurin inhibitors since rare case of lymphoma and malignancy have been described in patients treated with these agents. However, there is no evidence of systemic immune suppression or increased risk of malignancies in clinical trials followed-up to 4 years.^{113, 114} No case of skin malignancy or lymphoma have been described in patients with anogenital LS treated continuously with pimecrolimus cream 1% or tacrolimus ointment for long period of time.¹¹⁵ A controlled long-term post marketing study should be performed in order to clarify the real risk of developing lymphoma and malignancy.

Retinoids

TOPICAL RETINOIDS (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

In a case series of 22 patients a marked improvement of subjective symptoms and clinical scores, especially hyperkeratosis and erosions, was observed in more than 75% of the patients treated with 0.025% tretinoin once a day five days per week for one year.¹¹⁶

Another more recent case series investigated the alternate-day treatment with tretinoin 0.025% cream for 24 weeks of vulvar LS and concluded that topical tretinoin may be particularly useful for the treatment of hyperkeratotic forms of vulvar LS.⁷⁹

A recent study revealed that the application of 0.05% retinaldehyde twice per day for 30 days seems to restore the normal expression of CD44, which is decreased in LS.¹¹⁷

Two comparative trials confronting MF plus topical retinaldehyde with MF plus placebo for 6 months revealed that the combination with a topical retinoid did not enhance the effectiveness of a potent corticosteroid in the treatment of vulvar LS.^{118, 119}

Miscellaneous topical treatments

TOPICAL PREPARATIONS (VITAMIN E AND MOISTURIZERS) WERE FOUND HELPFUL IN SMALL CASE-SERIES.^{93, 120}

Non irritant non allergenic detergents could be suggested to the patients, in order to avoid further inflammation and provide symptomatic relief.

Phototherapy

UVA/PUVA (EVIDENCE LEVEL: 1+; RECOMMENDATION GRADE: B)

Few studies have investigated the use of ultraviolet (UV). In a pilot study, 5 women with vulvar LS were treated with cream containing 8-methoxypsoralen followed by UVA exposures. Two patients showed marked improvement with complete reduction in pruritus and an increase in tenderness, and one had a stable disease.¹²¹

A retrospective study showed an improvement of 10 patients of both sexes with UVA1.¹²² Seven women with severe genital LS not controlled by ultrapotent topical corticosteroids were treated with UVA1 and moderate and minimal improvement was seen in 3 and 2 patients, respectively. Two women with coexistent extragenital LS also received whole-body UVA1 treatment and extragenital lesions seemed to improve better than genital ones.¹²³

A comparative study of 30 patients with vulvar LS reported that UVA1 was inferior to topical CP 0.05% ointment.¹²⁴

PHOTODYNAMIC THERAPY (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Photodynamic therapy (PDT) seems to be a reasonably effective alternative therapeutic modality to treat vulvar LS and extragenital LS resistant to conventional treatment, as shown by several case series. Most patients experienced good symptomatic control of their disease, but only minimal change in clinical and histological appearance.^{125, 126}

A study included 100 women with genital LS treated with PDT. Partial or even full remission of subjective symptoms and objective clinical signs could be observed. After 6 courses of PDT the immunohistochemical staining in vulvar LS showed increasing microvessels density and decreasing lymphocytic infiltration.¹²⁷

When compared to CP (once daily for 8 weeks), 5-Aminolevulinic acid (ALA)-mediated photodynamic therapy (PDT) (ALA-PDT) (4 sessions) showed a longer remission duration and a higher complete response rate in vulvar LS. The short corticosteroid treatment duration could represent a bias which should be taken in consideration in interpreting the study results.¹²⁸

6.2 Systemic treatment

Glucocorticosteroids (Evidence level: 3; Recommendation grade: D)

Several retrospective studies support the efficacy of systemic corticosteroids plus methotrexate in LS patients resistant to topical treatments.¹²⁹

Oral retinoids (Evidence level: 1+; Recommendation grade: B)

Good results in the treatment of LS with oral etretinate were reported many years ago.^{130, 131} More recently, patients with genital LS were treated successfully with oral acitretin. In a multi-center trial of 78 patients with vulvar LS, a treatment with 20 to 30 mg/day of acitretin for 16 weeks led to some degree of improvement (especially in pruritus and burning sensation) in 2/3 of patients.¹³²

A study performed on 52 male patients with severe, long-standing LS resistant to topical treatment with ultrapotent corticosteroids showed a complete or partial response in 72% of the enrolled patients.¹³³

Other systemic therapy

CYCLOSPORINE (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Oral cyclosporine may be considered in refractory vulvar LS. Studies in adult men or children are not available.¹³⁴

METHOTREXATE (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Methotrexate between 10 and 15 mg/week for 6 months possibly combined with systemic steroids is reported to improve treatment resistant generalized cutaneous LS.¹³⁵

FUMARATES (EVIDENCE LEVEL: 3-4; RECOMMENDATION GRADE: D)

There are occasional observations of the successful use of fumarates in LS. Treatment with fumarate may be interesting for further evaluation.¹³⁶

ANTIBIOTICS (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Penicillins and cephalosporins (Ceftriaxone 1 g intramuscular every 2 weeks for three doses, and then once a month on as-needed basis (P.R.N.) or penicillin G benzathine suspension -long acting- 2.4 million units intramuscular every 2 weeks for three doses, and then once a month on P.R.N.) showed some improvement and may be considered in topical steroid resistant genital LS.¹³⁷

SULFASALAZINE (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Sulfasalazine (salazopyrine®) 1-2 g/day may be used in cutaneous LS.¹³⁸

6.3 Surgery

Male LS

Although widely used, the present knowledge of surgical procedures is based only on non-randomized studies and expert opinions.

CIRCUMCISION (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Most available studies suggests an early circumcision in boys in order to achieve a better prognosis or even a resolution of the disease.^{67, 80, 82, 139} A couple of studies point out the necessity of complete removal of the foreskin to prevent recurrence. A combination with steroid injections has been proposed, especially in those cases non limited to prepuce and glans only,¹⁴⁰ but further study are needed. 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 excision of the foreskin.

MEATAL DILATATION, MEATOTOMY, MEATOPLASTY (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Meatal involvement in LS is considered a negative prognostic factor since stenosis is a possible complication. Meatotomy or meatoplasty are possible surgical procedures with a good long-term follow-up.^{141, 142}

URETHROPLASTY (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

A large number of patients underwent early urethroplasty using buccal mucosa and the procedure was successful also at a long-term follow-up.^{67, 143} However, other surgical approaches for urethral stricture in LS have been proposed and the best treatment of is still matter of debate.¹⁴⁴

Female LS

Vulvectomy has been suggested as a possible treatment approach, particularly if malignant complications occurred.¹⁴⁵ In a retrospective study of 124 females, improvement was achieved in around 80 to 90% of patients with perineotomy.¹⁴⁶ Clitoral phimosis is the most distressing clinical picture because of pain or loss of sensitivity and various surgical techniques may be an option for selected patient.

VULVECTOMY (EVIDENCE LEVEL: 4; RECOMMENDATION GRADE: D)

Vulvectomy is an invasive intervention that is supported by some studies; however, they present a poor study design and both the long-term outcome and quality are still unknown.⁶⁶ Therefore, vulvectomy should be reserved only for LS associated with vulvar malignancy.

LABIAL, CLITORAL AND URETHRAL LESIONS (EVIDENCE LEVEL: 3; RECOMMENDATION GRADE: D)

Stenosis of the clitoral hood and labial adhesion are commons in LS. Long-term data of surgical procedure are available only in a few patients.^{66, 147-149}

6.4 CO₂ Laser (Evidence level: 3; Recommendation grade: D)

Case series studies have investigated the use of vaporization with CO₂ laser.¹⁵⁰⁻¹⁵² The rate of patients achieving good results after 2 months treatment was high and many patients still remained in remission after a follow-up period that range from 3 months to 7 years. However, several recurrences and complications have been reported.

6.5 Focused ultrasound (Evidence level: 3 Recommendation grade: D)

Focused ultrasound of white mucosal lesions improved itching and stimulated cell proliferation to repair the tissue damage. It may be reasonably considered another possible second-line treatment.^{153, 154}

6.6. Platelet-rich plasma and adipose-derived stem cells (Evidence level: 3-4 Recommendation grade: D)

A limited number of observational studies and case reports have recently assessed efficacy and safety of both adipose-derived stem cells (ADSCs) and platelet-rich plasma (PRP) for the treatment of genital LS.¹⁵⁵⁻¹⁵⁷ Both interventions improved short-term and patient-reported treatment outcomes. Thus, ADSCs and PRP may represent promising therapeutic perspectives, especially for scarring, atrophy and the other sequelae of genital LS that are poorly responsive to first-line topical treatments. Methodological biases, small case series, and lack of standardization of techniques and study outcome limit the relevance of these results. Further research, namely RCTs with long-term follow-up, is required for a better understanding of the available evidence.¹⁵⁸

7. Information for patients and general practitioners

LS is acknowledged the status of rare disease in Italy. Each regional health system organizes a register working on a dedicated web platform and it organizes a network of referral hospital centers for diagnosis, management and legal certification. LS number code is RL0060.

Patients affected by LS need regular clinical follow-up to monitor disease activity and efficacy of treatments and the cost is fully reimbursed by the Italian Health System (IHS). In case of off-label treatments, regional committees supervising the clinical network for rare diseases should approve the proposal and, in case of approval, the drug is given for free to the patient.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—All authors read and approved the final version of the manuscript.

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History.—Article first published online: April 29, 2021. - Manuscript accepted: March 23, 2021. - Manuscript revised: February 23, 2021. - Manuscript received: June 4, 2020.