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Evidence Report	**EuroGuiDerm** Centre for Guideline Development

EUROGUIDERM GUIDELINE ON LICHEN SCLEROSUS– EVIDENCE REPORT

Version 1.0, June 2023

Inhalt

1. Evidence to Decision framework

Question

What are the efficacy and safety of topical, systemic, interventional and operative therapies for the treatment of lichen sclerosus?	
Population:	Patients (all ages, all genders) with lichen sclerosus of all severities and localisations • Patients with anogenital and extragenital LS • Age groups to stratify for: (a) children (0-12), (b) adolescents (13-17), and (c) adults (≥18 years) • Pregnant women with lichen sclerosus

Intervention:	• Topical treatment
	  ○ Emollients
	  ○ Topical corticosteroids (TCS) and intralesional corticosteroids
	  ○ Topical calcineurin inhibitors
	  ○ Topical retinoids
	  ○ Topical hormone preparations
	• UV therapy
	• Photodynamic therapy (PDT)
	• Surgical interventions
	• Laser
	• Cryotherapy
	• Platelet rich plasma
	• Systemic treatment

Comparison:	Direct, placebo or no treatment
Main outcomes:	• Quality of Life (9 = critical) ○ Restoration of sexual function (9 = critical)

	○ Restoration of urinary function (7 = critical) • Symptoms ○ Improvement of symptoms (9 = critical) ○ Patient global assessment (5 = important) • Signs ○ Physician global assessment (6 = important) • Abolition of risk of cancer (9 = critical) • Adverse events ○ Minor adverse events (4 = important) ○ Serious adverse events (8 = critical) (Outcome domains adapted from 'Core Outcomes for Research in Lichen Sclerosus (CORALS)'[1]; outcome ranking adopted from BAD Guideline 2018[2])
Setting:	Region: Europe, dermatologists, gynaecologists, urologists, paediatrician, proctologists and general practitioners in clinical practice
Perspective:	Clinical recommendation – population perspective
Background:	• New evidence is available for the treatment of lichen sclerosus • Lichen sclerosus is underdiagnosed, and there is uncertainty about how best to diagnose and treat it[3, 4] • Several guidelines for the diagnosis and treatment of lichen sclerosus exist, but their recommendations vary and evidence-based recommendations are lacking • Different prescribing practices among dermatologists, gynaecologists and urologists and a lack of experience have been reported across Europe.[5, 6] There is a need for up-to-date, evidence-based guidance, diagnostic and treatment algorithms, and follow-up recommendations and distribution of this guidance • There is a lack of guidance on the interdisciplinary management of lichen sclerosus patients by dermatologists, urologists and gynaecologists
Study designs:	For the meta-analysis: • Randomised controlled trials

	• Prospective comparative cohort studies For descriptive results: • All trials (prospective and retrospective) with at least 10 participants per intervention
Conflict **of interests:**	No members of the guideline development committee declared that they had personal-financial (PF) interests. The EuroGuiDerm team also declared having no PF interests.
Procedure:	This evidence analysis is an update based on the systematic review of the BAD Guideline from 2018.[2] We have updated the search and updated the systematic review with data from studies published since 2017. Since the PICO is a bit narrower than the BAD guideline, a few studies that were included in the original BAD review were not included in this update. Please refer to the methods report for further details.

Assessment

Is the problem a priority?
Lichen sclerosus is one of the most common inflammatory diseases that affect the genital area. Despite this, there is limited data available regarding its prevalence or incidence. Wallace calculated a prevalence of 0.1–0.3% among all patients referred to a dermatology department in 1971.[7] A higher prevalence of vulval lichen sclerosus was found by Goldstein et al. in a general gynaecology practice, totalling 1.7% (28 of 1,675 patients) over a 3-year period.[8] In a Finnish registry study, Halonen et al. found that the incidence rate for lichen sclerosus increased from 14 per 100,000 woman-years in 2003 to 22 per 100,000 woman-years in 2010-2012.[9] Kizer et al. retrospectively examined 153,432 discharge records from male patients from 1997 to 1999 in a US Army hospital and calculated a lichen sclerosus incidence in male patients of 0.07%.[10] It is important to note, however, that the incidence and prevalence of lichen sclerosus are probably underestimated because the lesions can be asymptomatic or mild, and therefore patients may not notice them or not visit a doctor out of fear and embarrassment. In addition, even when patients with lichen sclerosus do present to their physicians, these providers (usually dermatologists, gynaecologists, urologists or general practitioners) often do not recognise LS or have little experience dealing with the disease.[3] When cases of lichen sclerosus are correctly diagnosed, there is often uncertainty about how best to treat the disease, including questions about which specialist should be in charge of managing the patient's treatment.[5, 6] However, timely and appropriate treatment are crucial because this can significantly reduce complications such as scarring and the development of anogenital carcinoma.[11] Lastly, studies show that many patients are dissatisfied with their therapy. In a Danish cross-sectional study, 265 patients with lichen sclerosus were asked about their satisfaction with their current therapy overall, and about their satisfaction with its effectiveness. In total, 28% of patients reported that they were dissatisfied with their treatment overall, and 58% reported that they were dissatisfied with the effectiveness of their therapy.[12]

Summing up, despite being a common inflammatory anogenital disease that usually follows a chronic course, the level of uncertainty surrounding its accurate diagnosis and treatment is high. Therefore, addressing this issue should be a priority.

Desirable Effects – How substantial are the desirable anticipated effects?

There were very few high-quality studies. In total, 14 trials[13-26] with 631 participants and one Cochrane review[27] (7 trials (6 female, 1 male) with 249 participants) met our inclusion criteria.
In total, 8 RCTs[13-17, 24-26] and one cohort study[18] looked at women, and one RCT included girls in addition to women.[19] One RCT looked at boys,[23] another RCT looked at men[21] and two further RCTs looked at men and women.[20, 22]

1. Systematic review

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	The review collects the type of studies you consider relevant to the guideline review question	The literature search is sufficiently rigorous to identify all the relevant studies	Study quality is assessed and reported	An adequate description of the methodology used is included, and the methods used are appropriate to the question	What types of studies are included in the review?
Chi, *Cochrane Database Syst Rev* 2011[27]	Yes	Yes	Yes	Yes	Yes	RCTs
COMMENTS: Cochrane review on the topical interventions for genital LS. Outcome measures listed mostly match those set in the guideline protocols. SUMMARY (modified from BAD GL 2018 Lewis et al.[2]):						

Seven RCTs ((6 women[28-33] and 1 boys)[34] with 249 participants) covering six treatments met the inclusion criteria. Six of these trials tested the efficacy of one active intervention against placebo or another active intervention, and the remaining trial tested three active interventions against placebo.

When compared to placebo in one trial (women), clobetasol propionate 0.05% was effective in treating vulval LS in relation to the outcomes 'participant-rated improvement or remission of symptoms' (risk ratio (RR) 2.85, 95% confidence interval (CI) 1.45 to 5.61) and 'investigator-rated global degree of improvement' (standardised mean difference (SMD) 5.74, 95% CI 4.26 to 7.23).[28]

When mometasone furoate 0.05% was compared to placebo in another trial (boys), there was a significant improvement in the 'investigator-rated change in clinical grade of phimosis' (SMD -1.04, 95% CI -1.77 to -0.31).[34]

Four trials (women) found no significant benefit for topical testosterone, dihydrotestosterone and progesterone.[28, 31-33] When used as maintenance therapy after an initial treatment with topical clobetasol propionate in another trial, topical testosterone worsened the symptoms (P <0.05), but placebo did not.[29]

One trial (women) found no difference between pimecrolimus and clobetasol propionate in relieving symptoms through change in pruritus (itching) (SMD -0.33, 95% CI -0.99 to 0.33) and burning/pain (SMD 0.03, 95% CI -0.62 to 0.69). However, pimecrolimus was less effective than clobetasol propionate with regard to the 'investigator-rated global degree of improvement' (SMD -1.64, 95% CI -2.40 to -0.87).[30]

The current limited evidence demonstrates the efficacy of clobetasol propionate, mometasone furoate, and pimecrolimus in treating genital LS. There was no substantial difference in the efficacy of relieving symptoms between pimecrolimus cream and clobetasol propionate, but the former was less effective in improving gross appearance (clinical signs).[27]

2. Prospective comparative trials

2.1. Women

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Topical vs. topical					
Ultrapotent TCS vs. potent TCS					
Clobetasol propionate vs. mometasone furoate					
Improvement of symptoms: (clinical resolution): clobetasol propionate vs. mometasone furoate (12 weeks)	54 Virgili 2014[13]	⊕⊕⊕⊕ High[a]	**RR 1.00** (0.83 to 1.21)	889 per 1,000	**0 fewer per 1,000** (151 fewer to 187 more)
Improvement of symptoms: (GOS 75) clobetasol propionate vs. mometasone furoate (12 weeks)	54 Virgili 2014[13]	⊕⊕◯◯ Low[b]	**RR 0.77** (0.41 to 1.44)	482 per 1,000	**111 fewer per 1,000** (284 fewer to 212 more)
Improvement of symptoms: (GSS 75) clobetasol propionate vs. mometasone furoate (12 weeks)	54 Virgili 2014[13]	⊕⊕◯◯ Low[b]	**RR 0.89** (0.59 to 1.34)	667 per 1,000	**73 fewer per 1,000** (273 fewer to 227 more)
Ultrapotent TCS vs. testosterone					
Clobetasol propionate vs. testosterone					

Improvement of symptoms: (complete response): clobetasol propionate vs. testosterone (3 months follow up)	40 Bornstein 1998[18]	⊕◯◯◯ Very low[b,c]	**RR 2.17** (1.03 to 4.55)	300 per 1,000	**351 more per 1,000** (9 more to 1,065 more)
Improvement of symptoms: (complete & incomplete response): clobetasol propionate vs. testosterone (1 year follow up)	40 Bornstein 1998[18]	⊕◯◯◯ Very low[c]	**RR 2.25** (1.29 to 3.92)	400 per 1,000	**500 more per 1,000** (116 more to 1,168 more)
Potent TCS vs. potent TCS					
Mometasone furoate 0.1% ointment (tapering) vs. mometasone furoate 0.1% ointment (continuous)					
Improvement of symptoms: (responders): mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)	64 Borghi 2015[14]	⊕⊕⊕◯ Moderate[b]	**RR 1.08** (0.85 to 1.37)	781 per 1,000	**62 more per 1,000** (117 fewer to 289 more)
Improvement of symptoms: (GOS 75) mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)	64 Borghi 2015[14]	⊕⊕⊕◯ Moderate[b]	**RR 1.67** (0.86 to 3.24)	281 per 1,000	**188 more per 1,000** (39 fewer to 629 more)
Improvement of symptoms: (GSS 75) mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)	64 Borghi 2015[14]	⊕⊕⊕◯ Moderate[b]	**RR 1.10** (0.77 to 1.57)	625 per 1,000	**63 more per 1,000** (144 fewer to 356 more)
UV therapy vs. topical					
UV therapy vs ultrapotent TCS					

UVA-1 home based phototherapy vs. clobetasol propionate 0.05% ointment					
Improvement of symptoms: (itching): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)	30 Terras 2014[15]	⊕⊕◯◯ Low[b,c]	-		The mean (itching) was **2.5 lower** (5.69 lower to 0.69 higher)
Improvement of symptoms: (burning/pain): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)	30 Terras 2014[15]	⊕◯◯◯ Very low[b,c]	-		The mean (burning/pain) was **1 lower** (4.1 lower to 2.1 higher)
Physician global assessment: (total clinicians score): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)	30 Terras 2014[15]	⊕◯◯◯ Very low[b,c]	-		The mean (total clinicians score) was **0.5 lower** (4.03 lower to 3.03 higher)
QoL: (Skindex-29 score): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)	30 Terras 2014[15]	⊕⊕◯◯ Low[b,c]	-		The mean (Skindex-29 score) was **24.7 lower** (50.17 lower to 0.77 higher)
Laser vs. topical					
Laser vs ultrapotent TCS					
CO2 laser vs. clobetasol propionate 0.05% ointment					
New: Improvement of symptoms (VAS itching): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VAS itching) was **1.43 lower** (3.22 lower to 0.36 higher)
New: Improvement of symptoms: (VAS burning): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VAS burning) was **1.78 lower** (3.69 lower to 0.13 higher)

New: Improvement of symptoms: (VAS irritation or tearing): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VAS irritation or tearing) was **2.83 lower** (4.73 lower to 0.93 lower)
New: Improvement of symptoms: (VAS tearing of vulval skin): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VAS tearing of vulval skin) was **0.45 lower** (2.56 lower to 1.66 higher)
New: Improvement of symptoms: (VAS painful defecation): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS painful defecation) was **0.11 lower** (1.62 lower to 1.4 higher)
New: Improvement of symptoms: (VSQ): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VSQ): was **3.34 lower** (5.91 lower to 0.77 lower)
New: Improvement of symptoms: (VHI): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VHI) was **2.35 higher** (0.16 higher to 4.54 higher)
New: Patient global assessment (PGI-I better or much better): CO2 laser vs. clobetasol propionate (6 months)	52 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	**RR 1.64** (1.09 to 2.46)	520 per 1,000	**333 more per 1,000** (47 more to 759 more)
New: Patient global assessment: (PGI-S satisfied or very satisfied): CO2 laser vs. clobetasol propionate (6 months)	52 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	**RR 2.16** (1.23 to 3.78)	360 per 1,000	**418 more per 1,000** (83 more to 1,001 more)
New: QoL: (Skindex-29): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕⊕◯ Moderate[b,c]	-		The mean (Skindex-29): CO2 laser vs. clobetasol propionate (6 months) was **10.91 lower** (18.12 lower to 3.7 lower)

New: Sexual function: (VAS pain with sex): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS pain with sex) was **0.55 lower** (1.79 lower to 0.69 higher)
New: Urinary function: (VAS dysuria): CO2 laser vs. clobetasol propionate (6 months)	51 Burkett, 2021[26]	⊕⊕◯◯ Low[b,c]	-		The mean (VAS dysuria) was **1.33 lower** (2.95 lower to 0.29 higher)
Laser vs potent TCS					
Nd:YAG laser vs. betamethasone					
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS burning decrease) was **1.2 higher** (1.42 lower to 3.82 higher)
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS burning decrease) was **1.4 higher** (1.16 lower to 3.96 higher)
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS burning decrease) was **2.7 higher** (0.35 higher to 5.05 higher
New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS itching decrease) was **2.3 higher** (0.39 lower to 4.99 higher)

New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS itching decrease) was **3 higher** (0.69 higher to 5.31 higher)
New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS itching decrease) was **1.9 higher** (2.7 lower to 6.5 higher)
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)	36 Bizjak Ogrinc, 2019[24]	⊕⊕◯◯ low[c]	-		The mean (VAS pain decrease) was **4.3 higher** (1.94 higher to 6.66 higher)
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS pain decrease) was **3.9 higher** (1.41 higher to 6.39 higher)
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (VAS pain decrease) was **3.4 higher** (1.6 lower to 8.4 higher)
New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)	36 Bizjak Ogrinc, 2019[24]	⊕◯◯◯ Very low[b,c]	-		The mean (sum score decrease) was **7.8 higher** (2.23 higher to 13.37 higher)

New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)	36 Bizjak Ogrinc, 2019[24]	⨁◯◯◯ Very low[b,c]	-		The mean (sum score decrease) was **8.4 higher** (3.7 higher to 13.1 higher)
New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)	36 Bizjak Ogrinc, 2019[24]	⨁◯◯◯ Very low[b,c]	-		The mean (sum score decrease) was **9 higher** (2.88 higher to 15.12 higher)
New: Improvement of symptoms: (sum score = 0): Nd:YAG laser vs. betamethasone (3 months)	40 Bizjak Ogrinc, 2019[24]	⨁◯◯◯ Very low[b,c]	**RR 17.00** (1.05 to 276.03)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
New: Physician global assessment: (mean improvement score): Nd:YAG laser vs. betamethasone (6 months)	31 Bizjak Ogrinc, 2019[24]	⨁◯◯◯ Very low[b,c]	-		The mean (mean improvement score) was **0.85 higher** (0.08 lower to 1.78 higher)
New: Patient global assessment: (very satisfied or satisfied): Nd:YAG laser vs. betamethason (3 months)	40 Bizjak Ogrinc, 2019[24]	⨁⨁◯◯ Low[b,c]	**RR 2.79** (1.93 to 2.85)	350 per 1,000	**627 more per 1,000** (325 more to 648 more)
Laser vs. placebo					
CO2 laser vs. sham laser					

New: Physician global assessment: (Providers' CSS): CO2 laser vs. sham laser (mean change from baseline at 6 months)	37 Mitchell, 2021[25]	⨁⨁◯◯ Low[b,c]	-		The mean (Providers' CSS) was **1 higher** (0.91 lower to 2.91 higher)
New: Patient global assessment: (Patients' CSS): CO2 laser vs. sham laser (mean change from baseline at 6 months)	37 Mitchell, 2021[25]	⨁◯◯◯ Very low[b,c]	-		The mean (Patients' CSS) was **2.3 lower** (9.65 lower to 5.05 higher)
Photodynamic therapy vs. topical					
Photodynamic therapy vs. ultrapotent TCS					
ALA-PDT vs. clobetasol propionate 0.05% ointment					
Improvement of symptoms: (complete and partial response): ALA-PDT vs. clobetasol propionate (8 weeks)	43 Shi 2016[16]	⨁⨁◯◯ Low[b,c]	**RR 1.45** (0.98 to 2.14)	591 per 1,000	**266 more per 1,000** (12 fewer to 674 more)
Systemic treatment vs. placebo					
Acitretin p.o. vs. placebo					
Improvement of symptoms: (responders): acitretin vs. placebo (16 weeks)	78 Bousema 1994[17]	⨁⨁⨁◯ Moderate[b]	**RR 2.33** (1.00 to 5.44)	154 per 1,000	**205 more per 1,000** (0 fewer to 684 more)
Patient global assessment: (partially or completely satisfied): acitretin vs. placebo (16 weeks)	78 Bousema 1994[17]	⨁⨁⨁◯ Moderate[b]	**RR 1.52** (1.15 to 2.02)	590 per 1,000	**307 more per 1,000** (88 more to 602 more)

Explanations
a. No clinical important difference – CI is between minimally important differences (MIDs)
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs
c. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias

2.2. Girls
No data

2.3. Women and girls

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Topical vs. topical					
Ultrapotent TCS vs. TCI					
Clobetasol propionate vs. tacrolimus					
Improvement of symptoms: clobetasol propionate vs. tacrolimus (3 months)	58 Funaro, 2014[19]	⨁⨁⨁◯ Moderate[a,b]	**RR 0.96** (0.85 to 1.09)	966 per 1,000	**39 fewer per 1,000** (145 fewer to 87 more)

Improvement of symptoms: (absence of symptoms): clobetasol propionate vs. tacrolimus (2 months)	58 Funaro, 2014[19]	⊕⊕⊕◯ Moderate[a]	**RR 3.75** (1.41 to 9.95)	138 per 1,000	**380 more per 1,000** (57 more to 1,235 more)
a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias b. No clinically important difference – CI was between MIDs					

2.4. Men

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Systemic treatment vs. placebo					
Acitretin vs. placebo					
QoL (DLQI): acitretin vs. placebo (mean change from baseline at 20 weeks)	51 Ioannides, 2010[21]	⊕⊕⊕◯ Moderate[a]	-		The mean QoL (DLQI) was **4.2 lower** (6.68 lower to 1.72 lower)

Improvement of symptoms: (complete response): acitretin vs. placebo (20 weeks)	51 Ioannides, 2010[21]	⊕⊕⊕◯ Moderate[a]	**RR 6.00** (0.85 to 42.39)	59 per 1,000	**295 more per 1,000** (9 fewer to 2,442 more)
Physician global assessment (total clinical score): acitretin vs. placebo (mean change from baseline at 20 weeks)	51 Ioannides, 2010[21]	⊕⊕⊕⊕ High	-		The mean physician global assessment (total clinical score) was **4.9 lower** (7 lower to 2.8 lower)
a. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs					

2.5. Boys

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Surgery vs. surgery					
Circumcision vs. preputioplasty and intralesional triamcinolone (PIT)					
New: Patient global assessment: (very satisfied or satisfied with treatment): circumcision vs. PIT (1 year)	19 Lansdale, 2021[23]	⊕◯◯◯ Very low[a,b]	**RR 0.43** (0.12 to 1.48)	667 per 1,000	**380 fewer per 1,000** (587 fewer to 320 more)

New: Patient global assessment: (very satisfied or satisfied with cosmetic outcome): circumcision vs. PIT (1 year)	19 Lansdale, 2021[23]	⊕◯◯◯ Very low[a,b]	**RR 0.49** (0.14 to 1.74)	583 per 1,000	**298 fewer per 1,000** (502 fewer to 432 more)
New: Patient global assessment: (very satisfied or satisfied with treatment of symptoms): circumcision vs. PIT (1 year)	19 Lansdale, 2021[23]	⊕◯◯◯ Very low[a,b]	**RR 0.57** (0.16 to 2.10)	500 per 1,000	**215 fewer per 1,000** (420 fewer to 550 more)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

2.6. Mixed (children)
No data

2.7. Mixed (adults)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Systemic treatment vs. placebo					
Paraminobenzote vs. placebo					

Improvement of symptoms (marked, moderate or slight improvement) paraminobenzote vs. placebo (2 months)	25 Buxton 1990[20]	⊕◯◯◯ Very low[a,b]	**RR 0.93** (0.44 to 1.98)	539 per 1,000	**38 fewer per 1,000** (302 fewer to 528 more)
Surgery vs. Surgery + PRP					
Adipose tissue derived-stromal vascular fraction (AD-SVF) vs. adipose tissue derived-stromal vascular fraction (AD-SVF)+PRP					
New: Improvement of symptoms (progressive decrease in symptoms until they disappeared): AD-SVF vs. AD-SVF+PRP (6 months)	40 Tedesco, 2020[22]	⊕◯◯◯ Very low[a,b]	**RR 0.86** (0.35 to 2.10)	350 per 1,000	**49 fewer per 1,000** (227 fewer to 385 more)
New: QoL (DLQI): AD-SVF vs. AD-SVF+PRP (6 months)	40 Tedesco, 2020[22]	⊕⊕◯◯ Low[a]	-		The mean new: QoL (DLQI) was **3.4 lower** (4.91 lower to 1.89 lower)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

2.8. Mixed (children and adults)
No trials

Undesirable Effects – How substantial are the undesirable anticipated effects?

There were very few high-quality studies. In total, 14 trials[13-26] with 631 participants and one Cochrane review[27] (7 trials (6 female, 1 male) with 249 participants) met our inclusion criteria.
In total, 8 RCTs[13-17, 24-26] and one cohort study[18] looked at women, and one RCT included girls in addition to women.[19] One RCT looked at boys,[23] another RCT looked at amen[21] and two further RCTs looked at male and female adults.[20, 22]

1. Systematic reviews

STUDY	The review addresses an appropriate and clearly focused question that is relevant to the guideline review question	The review collects the type of studies you consider relevant to the guideline review question	The literature search is sufficiently rigorous to identify all the relevant studies	Study quality is assessed and reported	An adequate description of the methodology used is included, and the methods used are appropriate to the question	What types of studies are included in the review?
Chi, *Cochrane Database Syst Rev* 2011[27]	Yes	Yes	Yes	Yes	Yes	RCTs

COMMENTS:

Cochrane review on topical interventions for genital LS. Outcome measures listed mostly match those set in the guideline protocols.

SUMMARY:

Seven trials (6 women[28-33] and 1 boys[34]) with 249 participants covering six treatments met the inclusion criteria. Six of these RCTs tested the efficacy of one active intervention against placebo or another active intervention, whereas the remaining trial tested three active interventions against placebo.

Two trials (clobetasol propionate 0.05% vs. placebo and mometasone furoate 0.05% vs. placebo) found no significant differences in reported adverse drug reactions between the TCS and placebo groups.[28, 34] Another trial found no significant differences in reported adverse drug reactions between pimecrolimus and clobetasol propionate 0.05%.[30] Furthermore, two studies that compared topical testosterone against placebo showed no significant differences in severe adverse drug reactions when the studies were combined .[28, 33] In a further trial, no significant differences in adverse drug reactions were found between testosterone and clobetasol propionate with regard to the outcomes 'adverse drug reactions that were severe enough to require withdrawal of treatment' or 'adverse drug reactions that were not severe enough to require cessation of treatment'.[28]

2. Prospective comparative trials

1.1. Women

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Systemic treatment vs. placebo					
Acitretin vs. placebo					
Minor adverse events: acitretin vs. placebo (16 weeks)	78 Bousema 1994[17]	⨁⨁⨁⨁ High	**RR 1.93** (1.42 to 2.61)	513 per 1.000	**477 more per 1.000** (215 more to 826 more)
Laser vs topical					
Laser vs ultrapotent TCS					
CO2 laser vs. clobetasol propionate					
New: Patients with minor adverse events: CO2 laser vs. clobetasol propionate (6 months)	51 Burkett,2021[26]	⨁◯◯◯ Very low[b,c]	**RR 0.89** (0.06 to 13.45)	42 per 1.000	**5 fewer per 1.000** (39 fewer to 519 more)

1.2. Girls
No data

1.3. Women and girls
No data

1.4. Men
No data

1.5. Boys

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with control*	Risk difference (95% CI)**
*Risk of occurrence of the outcome with the control intervention (control intervention is the second named intervention) **Describes the actual difference in the observed risk of events between experimental and control interventions					
Surgery vs. surgery					
Circumcision vs. preputioplasty and intralesional triamcinolone (PIT)					
New: Patients with minor adverse events: circumcision vs. PIT (1 year)	19 Lansdale, 2021[23]	⨁◯◯◯ Very low[a,b]	**RR 1.71** (0.13 to 23.32)	83 per 1,000	**59 more per 1,000** (73 fewer to 1,860 more)

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias

b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs
1.6. Men and boys No data
1.7. Mixed (adults) No data
1.8. Mixed (children) No data
1.9. Mixed (adults and children) No data

Values: Is there important uncertainty about or variability in how much people value the main outcomes?

• Quality of Life
  ○ Restoration of sexual function
  ○ Restoration of urinary function
• Symptoms
  ○ Improvement of symptoms
  ○ Patient global assessment
• Signs

- Physician global assessment
- Abolition of risk of cancer
- Adverse events
  - Minor adverse events
  - Serious adverse events

There is a broad range of outcomes and measures that have been used to assess the impact, activity and severity of lichen sclerosus[35], these have not been defined or applied in standardised or consistent way, making comparisons difficult. A recent initiative, CORALS, aims to develop an internationally accepted 'core outcome set' (COS) for use in all future LS trials. Outcomes consist of 'domains' (what to measure) and 'instruments' (how to measure). Consensus was met in 2022 for '*quality of life – LS specific'*, '*symptoms'* and '*clinical (visible) signs'*. The next steps will be to agree which instruments should be used to measure these domains (ISSVD 2022, publication in preparation).

Resources required: How large are the resource requirements (costs)?
There are no studies looking at costs or economic evaluations. Resource use and costs vary by country and health system, making such analyses difficult. However, most topical therapies, such as clobetasol propionate, are comparatively inexpensive.

Cost effectiveness: Does the cost-effectiveness of the intervention favour one of the above interventions over another?
Resource use and costs vary according to country and health care system, making extrapolation from one setting to another difficult. Emollients and TCS are usually less expensive than other topical therapies or interventional or systemic treatments.
Equity: What would be the impact on health equity?

In a cross-sectional study from 2015 in which 128 gynaecologists and dermatologists were asked how they treat patients with lichen sclerosus, it was shown that treatment varies significantly among experts. There are both significant treatment differences between each primary treating specialty and between physicians practising in different geographic locations.[6]

In a follow-up of 48 patients with anogenital lichen sclerosus who visited the outpatient departments of obstetrics and gynaecology or dermatology of a university hospital in the Netherlands between 1995 and 2001, it was found that LS patients in the gynaecology department more often received surgical treatment, topical oestrogens and lidocaine ointment, whereas in the dermatology department patients were more frequently prescribed local moderate and poten TCS (class 2,3).[5]

The guideline development group felt that inequalities would be reduced if there were clear recommendations to form a diagnostic and treatment algorithm for lichen sclerosus for all specialties.

Acceptability: Is the intervention acceptable to key stakeholders?

In a cross-sectional survey of 128 gynaecologists and dermatologists from 2015, Selk found that clobetasol propionate 0.05% was the most commonly used first-line agent for lichen sclerosus (85%). The most commonly used second-line agents were tacrolimus (39%), other topical steroids (28%) and intralesional steroids (13%).[6]

However, concerns about the side effects of preparations containing topical cortisone have a negative impact on the acceptance of treatment among patients and physicians, as well as on patient compliance.[36] Several studies suggest that compliance rates in patients treated for lichen sclerosus are relatively low.

In a prospective longitudinal cohort study of 507 vulval lichen sclerosus patients treated with TCS, 150 patients reported that they followed treatment instructions only ‘some of the time’, ‘little of the time’ or ‘none of the time’. Accordingly, the compliance rate was only 70.4%. Reasons for not following the treatment recommendations were not given in the study.[11]

In another, prospective cross-sectional study with vulval lichen sclerosus patients treated with TCS, 31 of 136 patients reported that they followed treatment instructions only ‘most days’, ‘some days’ or ‘not at all’. Accordingly, the compliance rate in this study was also only 77.2%. Again, the reasons for the non-compliance were not reported.[37]

In a 52-week maintenance phase in which 44 patients with vulval lichen sclerosus were treated twice weekly with topical clobetasol propionate ointment 0,05% or mometasone furoate ointment, 40 patients (90.9%) adhered to therapy, whereas four (2 from each group) did not.[38]

In a retrospective chart review of 129 adult patients with vulval lichen sclerosus, 84 (65%) patients reported being compliant with treatment with TCS.[39]

In a retrospective chart review of case records of girls with vulval lichen sclerosus, 84 (71.2%) of 118 patients were compliant and used treatment regularly as instructed. For non-compliance, the most common reasons were 'unspecified' or the 'patient's desire for autonomy'. Parental corticosteroid phobia led to non-compliance in three patients.[40]

In a second retrospective study with 46 girls with prepubertal-onset vulval lichen sclerosus, 13 (28.7%) patients were not adherent to long-term treatment with TCS, whereas 33 patients (71.3%) reported that they used the treatment all or most of the time.[41]

Feasibility: Is the intervention feasible to implement?

Physicians must be trained in dealing with lichen sclerosus so it can be correctly diagnosed and adequately treated. All recommended treatments are available and accessible in Europe.

Because lichen sclerosus is a chronic disease that often requires long-term treatment, it is important that patients are adequately informed about the disease. Patients need to be informed about treatment options, as well as the increased risk of irreversible damage in bad treatment adhearance.

2. Appendix A: Forest plots

a. Women

Topical vs. topical

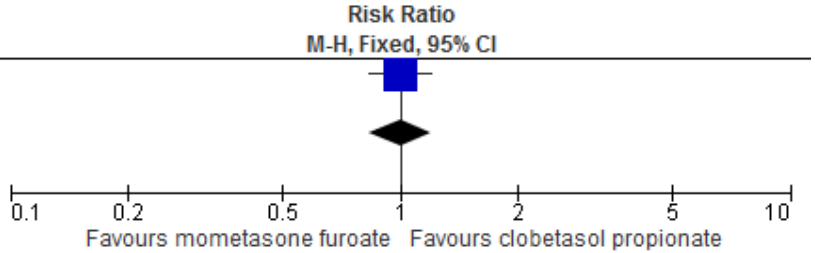
Ultrapotent TCS vs. potent TCS

Clobetasol proprionate 0.05% ointment vs. mometasone furoate 0.1% ointment

- **Decrease in symptoms and signs of LS (improvement of symptoms) (12 weeks)**

Study or Subgroup	Clobetasol propionate Events	Total	Mometasone furoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Virgili, BJD 2014	24	27	24	27	100.0%	1.00 [0.83, 1.21]
Total (95% CI)		**27**		**27**	**100.0%**	**1.00 [0.83, 1.21]**
Total events	24		24			

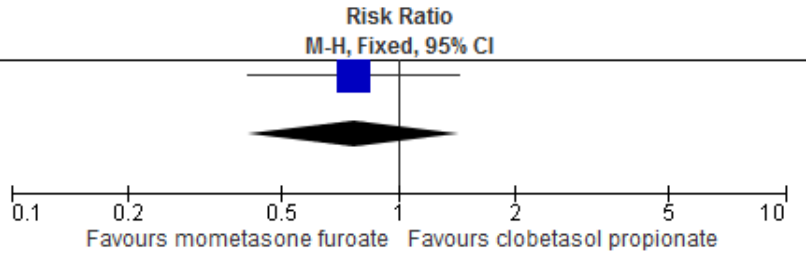
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



- **Achieving an improvement from baseline of ≥ 75% in objective scores - GOS 75 (improvement of symptoms) (12 weeks)**

Study or Subgroup	Clobetasol propionate Events	Total	Mometasone furoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Virgili, BJD 2014	10	27	13	27	100.0%	0.77 [0.41, 1.44]
Total (95% CI)		**27**		**27**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	10		13			

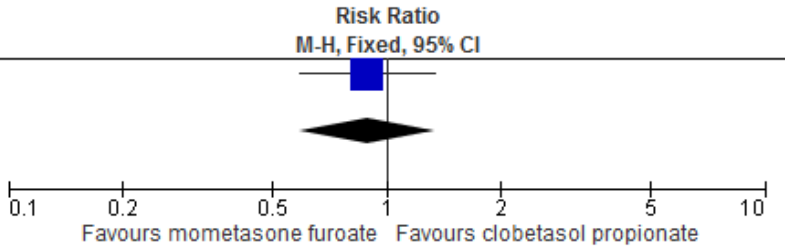
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



- **Achieving an improvement from baseline of ≥ 75% in subjective scores - GSS 75 (improvement of symptoms) (12 weeks)**

Study or Subgroup	Clobetasol propionate Events	Total	Mometasone furoate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Virgili, BJD 2014	16	27	18	27	100.0%	0.89 [0.59, 1.34]
Total (95% CI)		**27**		**27**	**100.0%**	**0.89 [0.59, 1.34]**
Total events	16		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)



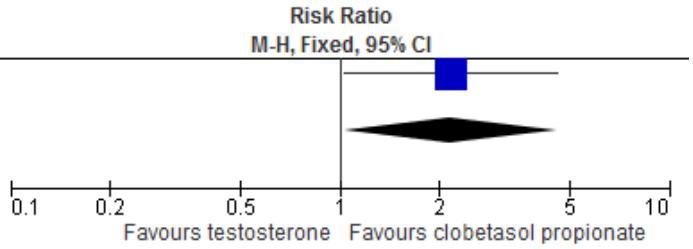
Ultrapotent TCS vs. testosteron

Clobetasol proprionate 0.05% ointment vs. testosterone 2% in petrolatum

- **Complete response (improvement of symptoms) (3 month follow-up)**

Study or Subgroup	Clobetasol propionate Events	Total	Testosterone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bornstein, Am J Obstet Gynaecol 1998	13	20	6	20	100.0%	2.17 [1.03, 4.55]
Total (95% CI)		**20**		**20**	**100.0%**	**2.17 [1.03, 4.55]**
Total events	13		6			

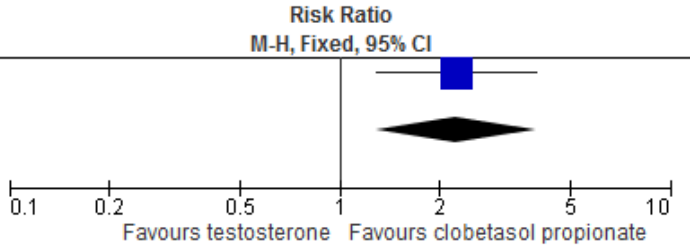
Heterogeneity: Not applicable
Test for overall effect: Z = 2.04 (P = 0.04)



- **All responses - Partial/Complete (improvement of symptoms) (1 year follow-up)**

Study or Subgroup	Clobetasol propionate Events	Total	Testosterone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bornstein, Am J Obstet Gynaecol 1998	18	20	8	20	100.0%	2.25 [1.29, 3.92]
Total (95% CI)		**20**		**20**	**100.0%**	**2.25 [1.29, 3.92]**
Total events	18		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.86 (P = 0.004)



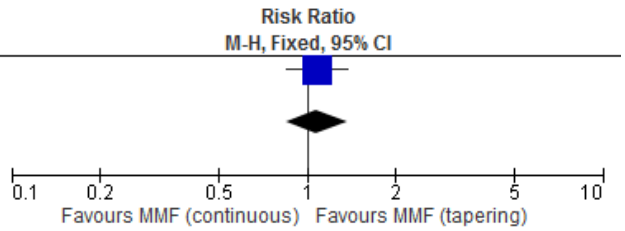
Potent TCS vs. potent TCS

Mometasone furoate 0.1% ointment (tapering) vs. mometasone furoate 0.1% ointment (continuous)

- **Responders (Improvement of symptoms) (3 months)**

Study or Subgroup	Mometasone furoate (tapering) Events	Total	Mometasone furoate (continuous) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borghi, BJD 2015	27	32	25	32	100.0%	1.08 [0.85, 1.37]
Total (95% CI)		**32**		**32**	**100.0%**	**1.08 [0.85, 1.37]**
Total events	27		25			

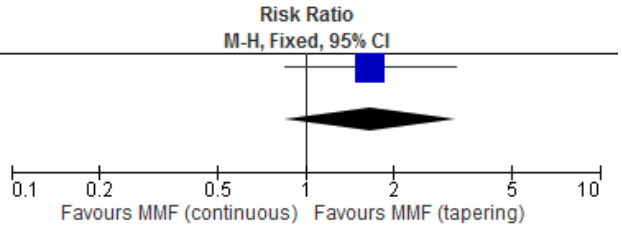
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)



- **Achieving an improvement from baseline of ≥ 75% in objective scores - GOS 75 (improvement of symptoms) (3 months)**

Study or Subgroup	Mometasone furoate (tapering) Events	Total	Mometasone furoate (continuous) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borghi, BJD 2015	15	32	9	32	100.0%	1.67 [0.86, 3.24]
Total (95% CI)		**32**		**32**	**100.0%**	**1.67 [0.86, 3.24]**
Total events	15		9			

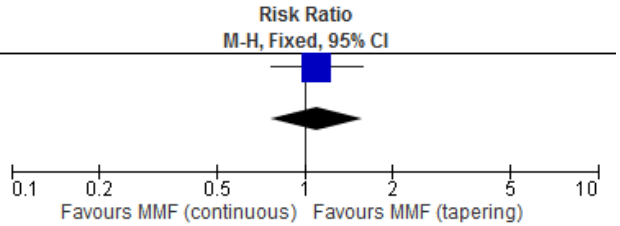
Heterogeneity: Not applicable
Test for overall effect: Z = 1.50 (P = 0.13)



- **Achieving an improvement from baseline of ≥ 75% in subjective scores - GSS 75 (improvement of symptoms) (3 months)**

Study or Subgroup	Mometasone furoate (tapering) Events	Total	Mometasone furoate (continuous) Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borghi, BJD 2015	22	32	20	32	100.0%	1.10 [0.77, 1.57]
Total (95% CI)		**32**		**32**	**100.0%**	**1.10 [0.77, 1.57]**
Total events	22		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.60)



UV vs. topical

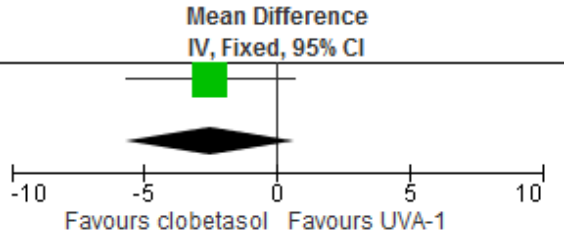
UV vs ultrapotent TCS

UVA-1 home based phototherapy vs. clobetasol propionate 0.05% ointment

- **VAS itching mean decrase from baseline (improvement of symptoms) (3 months)**

Study or Subgroup	UVA-1 Mean	UVA-1 SD	UVA-1 Total	Clobetasol Mean	Clobetasol SD	Clobetasol Total	Weight	Mean Difference IV, Fixed, 95% CI
Terras, JAMA Dermatol 2014	2.1	2.8892	15	4.6	5.5979	15	100.0%	-2.50 [-5.69, 0.69]
Total (95% CI)			**15**			**15**	**100.0%**	**-2.50 [-5.69, 0.69]**

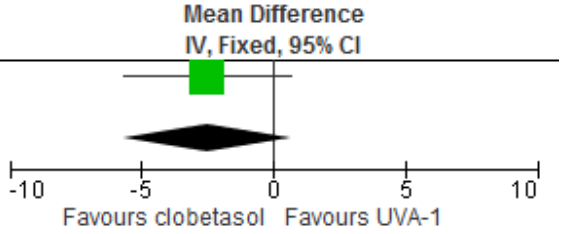
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)



- **VAS burning and/or pain mean decrase from baseline (improvement of symptoms) (3 months)**

Study or Subgroup	UVA-1 Mean	UVA-1 SD	UVA-1 Total	Clobetasol Mean	Clobetasol SD	Clobetasol Total	Weight	Mean Difference IV, Fixed, 95% CI
Terras, JAMA Dermatol 2014	2.1	2.8892	15	4.6	5.5979	15	100.0%	-2.50 [-5.69, 0.69]
Total (95% CI)			**15**			**15**	**100.0%**	**-2.50 [-5.69, 0.69]**

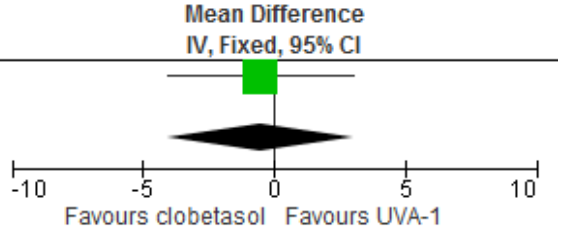
Heterogeneity: Not applicable
Test for overall effect: Z = 1.54 (P = 0.12)



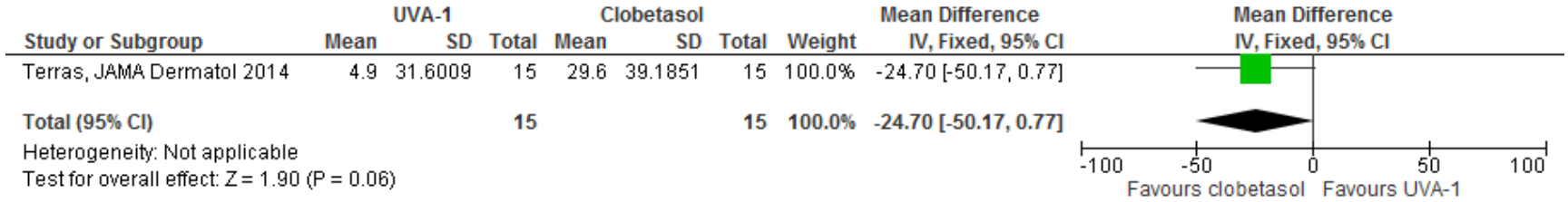
- **Total clinicians score – TCS mean decrase from baseline (Physician global assessment) (3 months)**

Study or Subgroup	UVA-1 Mean	UVA-1 SD	UVA-1 Total	Clobetasol Mean	Clobetasol SD	Clobetasol Total	Weight	Mean Difference IV, Fixed, 95% CI
Terras, JAMA Dermatol 2014	4.5	5.5979	15	5	4.1533	15	100.0%	-0.50 [-4.03, 3.03]
Total (95% CI)			**15**			**15**	**100.0%**	**-0.50 [-4.03, 3.03]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)



- **Skindex-29 score at end of treatment mean decrase from baseline (QoL) (3 months)**

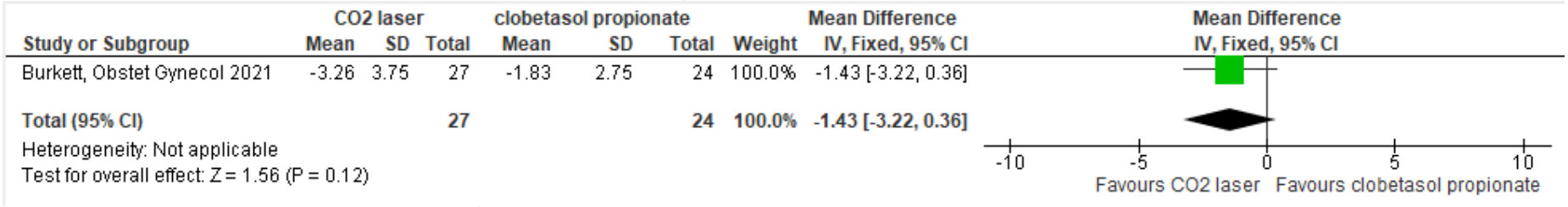


Laser vs. topical

Laser vs. ultrapotent TCS

CO2 laser vs. clobetasol propionate 0.05% ointment

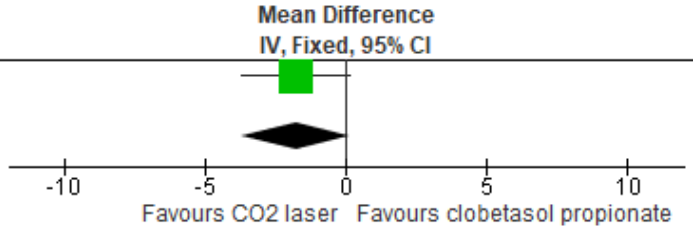
- **(New) VAS itching mean difference from baseline (improvement of symptoms) (6 months)**



- **(New) VAS burning mean difference from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	CO2 laser Mean	SD	Total	clobetasol propionate Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-2.78	3.76	27	-1	3.21	24	100.0%	-1.78 [-3.69, 0.13]
Total (95% CI)			**27**			**24**	**100.0%**	**-1.78 [-3.69, 0.13]**

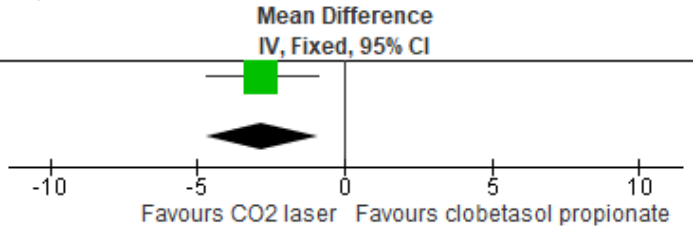
Heterogeneity: Not applicable
Test for overall effect: Z = 1.82 (P = 0.07)



- **(New) VAS irritation or tearing mean difference from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	CO2 laser Mean	SD	Total	clobetasol propionate Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-4.15	4.04	27	-1.32	2.84	24	100.0%	-2.83 [-4.73, -0.93]
Total (95% CI)			**27**			**24**	**100.0%**	**-2.83 [-4.73, -0.93]**

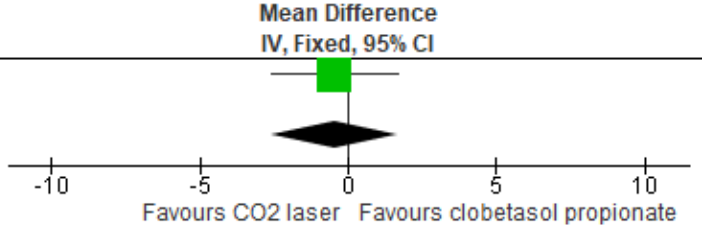
Heterogeneity: Not applicable
Test for overall effect: Z = 2.92 (P = 0.004)



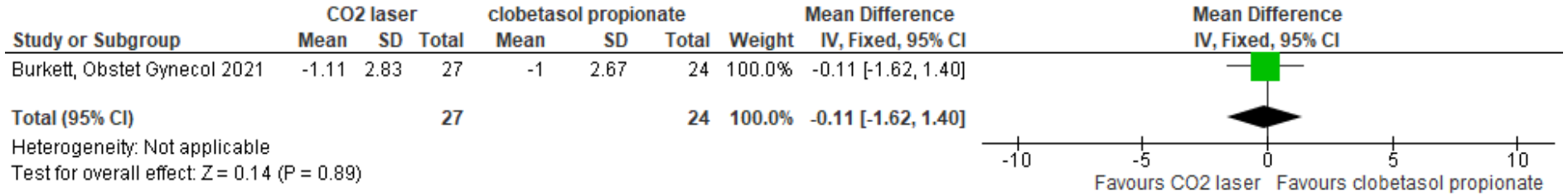
- **(New) VAS tearing of vulval skin mean difference from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	CO2 laser Mean	SD	Total	clobetasol propionate Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-1.77	3.55	27	-1.32	4.07	24	100.0%	-0.45 [-2.56, 1.66]
Total (95% CI)			**27**			**24**	**100.0%**	**-0.45 [-2.56, 1.66]**

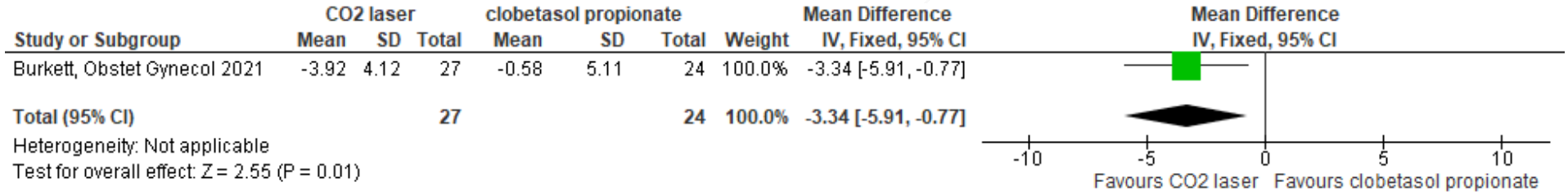
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)



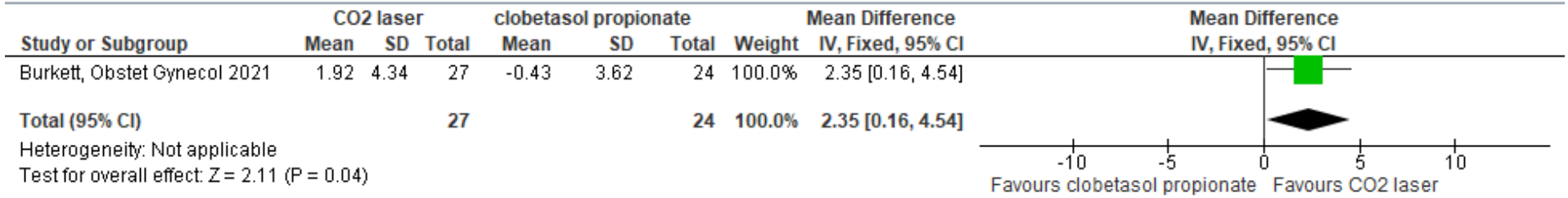
- **(New) VAS painful defecation mean difference from baseline (improvement of symptoms) (6 months)**



- **(New) Vulvovaginal symptoms questionnaire - VSQ mean difference from baseline (improvement of symptoms) (6 months)**



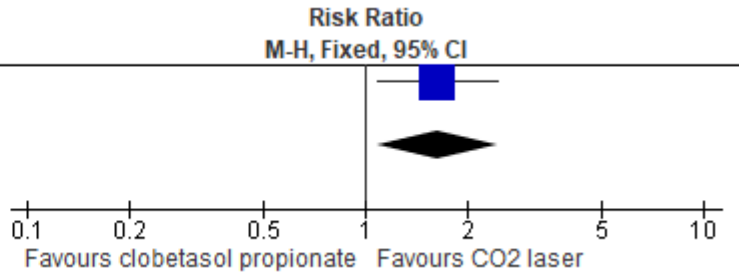
- **(New) Vaginal health index - VHI mean difference from baseline (improvement of symptoms) (6 months)**



- **(New) patient global impression of improvement - PGI-I better or much better (patient global assessment) (6 months)**

Study or Subgroup	CO2 laser Events	Total	clobetasol propionate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	23	27	13	25	100.0%	1.64 [1.09, 2.46]
Total (95% CI)		**27**		**25**	**100.0%**	**1.64 [1.09, 2.46]**
Total events	23		13			

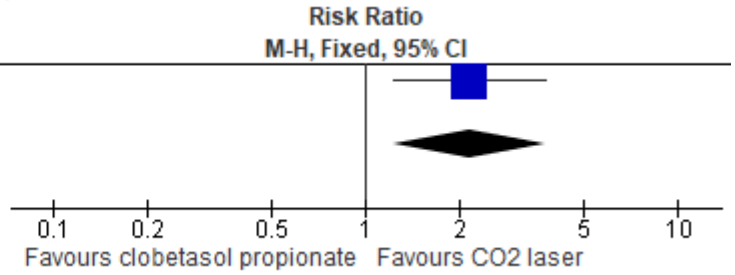
Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)



- **(New) patient global impression of severity - PGI-S satisfied or very satisfied (patient global assessment) (6 months)**

Study or Subgroup	CO2 laser Events	Total	clobetasol propionate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	21	27	9	25	100.0%	2.16 [1.23, 3.78]
Total (95% CI)		**27**		**25**	**100.0%**	**2.16 [1.23, 3.78]**
Total events	21		9			

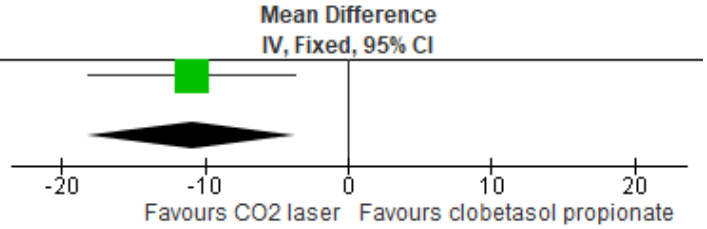
Heterogeneity: Not applicable
Test for overall effect: Z = 2.70 (P = 0.007)



- **(New) Skindex 29 mean change from baseline (quality of life) (6 months)**

Study or Subgroup	CO2 laser Mean	SD	Total	clobetasol propionate Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-16.83	18.09	27	-5.92	5.81	24	100.0%	-10.91 [-18.12, -3.70]
Total (95% CI)			**27**			**24**	**100.0%**	**-10.91 [-18.12, -3.70]**

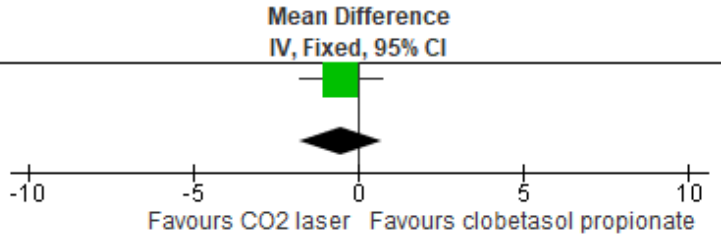
Heterogeneity: Not applicable
Test for overall effect: Z = 2.97 (P = 0.003)



- **(New) VAS pain with sex mean change from baseline (restoration of sexual function) (6 months)**

	CO2 laser			clobetasol propionate				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-0.69	2.95	27	-0.14	1.35	24	100.0%	-0.55 [-1.79, 0.69]
Total (95% CI)			**27**			**24**	**100.0%**	**-0.55 [-1.79, 0.69]**

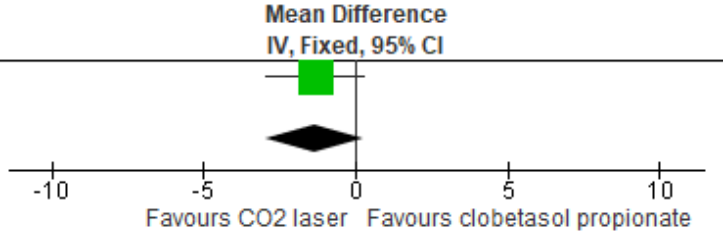
Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)



- **(New) VAS dysuria mean change from baseline (restoration of urinary function) (6 months)**

	CO2 laser			clobetasol propionate				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	-2.11	3.47	27	-0.78	2.37	24	100.0%	-1.33 [-2.95, 0.29]
Total (95% CI)			**27**			**24**	**100.0%**	**-1.33 [-2.95, 0.29]**

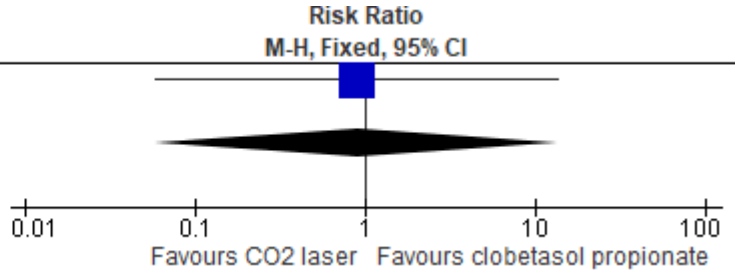
Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)



- **(New) patients with minor adverse events (6 months)**

	CO2 laser		clobetasol propionate			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Burkett, Obstet Gynecol 2021	1	27	1	24	100.0%	0.89 [0.06, 13.45]
Total (95% CI)		**27**		**24**	**100.0%**	**0.89 [0.06, 13.45]**
Total events	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.08 (P = 0.93)



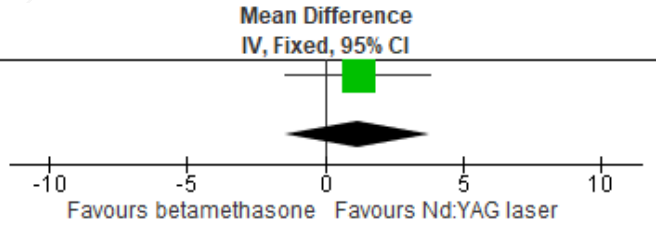
Laser vs. potent TCS

Nd:YAG laser vs. betamethasone

- **(New) VAS burning decrease from baseline (improvement of symptoms) (1 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	Betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	4.9	4.2734	20	3.7	3.7533	16	100.0%	1.20 [-1.42, 3.82]
Total (95% CI)			**20**			**16**	**100.0%**	**1.20 [-1.42, 3.82]**

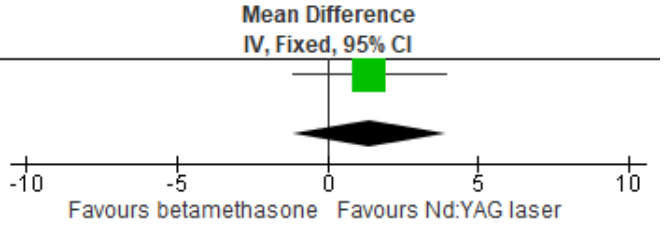
Heterogeneity: Not applicable
Test for overall effect: Z = 0.90 (P = 0.37)



- **(New) VAS burning decrease from baseline (improvement of symptoms) (3 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	5	4.0597	20	3.6	3.7533	16	100.0%	1.40 [-1.16, 3.96]
Total (95% CI)			**20**			**16**	**100.0%**	**1.40 [-1.16, 3.96]**

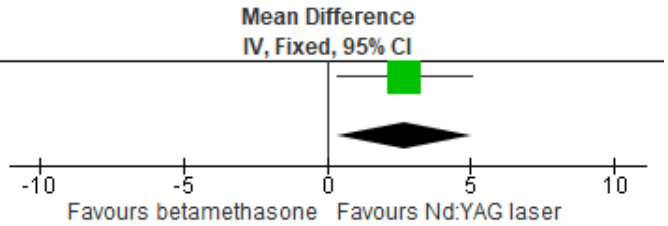
Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.28)



- **(New) VAS burning decrease from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	4.4	4.487	20	1.7	2.6273	16	100.0%	2.70 [0.35, 5.05]
Total (95% CI)			**20**			**16**	**100.0%**	**2.70 [0.35, 5.05]**

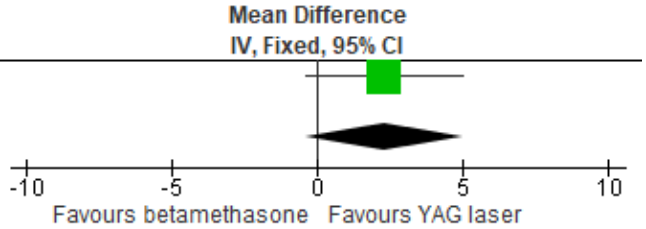
Heterogeneity: Not applicable
Test for overall effect: Z = 2.25 (P = 0.02)



- **(New) VAS itching decrease from baseline (improvement of symptoms) (1 month)**

Study or Subgroup	YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	6.1	4.2734	20	3.8	3.941	16	100.0%	2.30 [-0.39, 4.99]
Total (95% CI)			**20**			**16**	**100.0%**	**2.30 [-0.39, 4.99]**

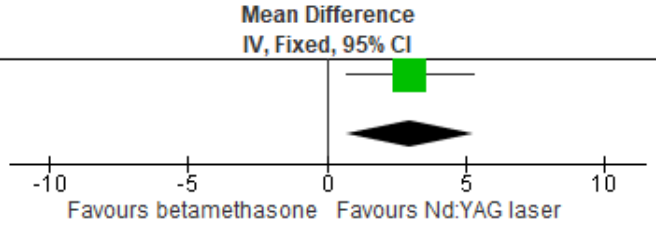
Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



- **(New) VAS itching decrease from baseline (improvement of symptoms) (3 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	6.4	4.0597	20	3.4	3.0027	16	100.0%	3.00 [0.69, 5.31]
Total (95% CI)			**20**			**16**	**100.0%**	**3.00 [0.69, 5.31]**

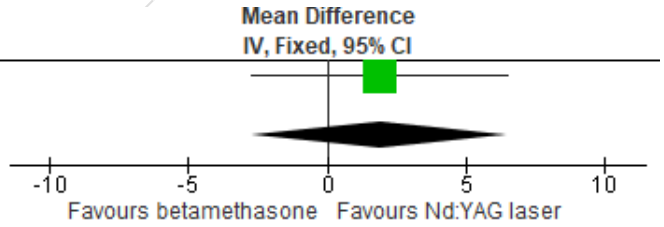
Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)



- **(New) VAS itching decrease from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	4.9	5.3417	20	3	8.0696	16	100.0%	1.90 [-2.70, 6.50]
Total (95% CI)			**20**			**16**	**100.0%**	**1.90 [-2.70, 6.50]**

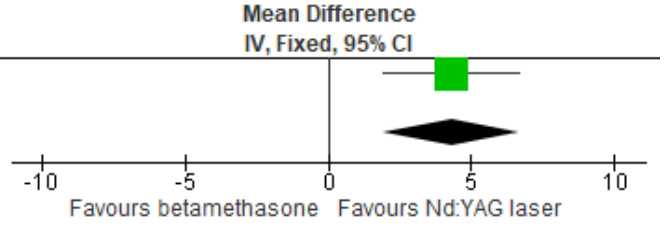
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)



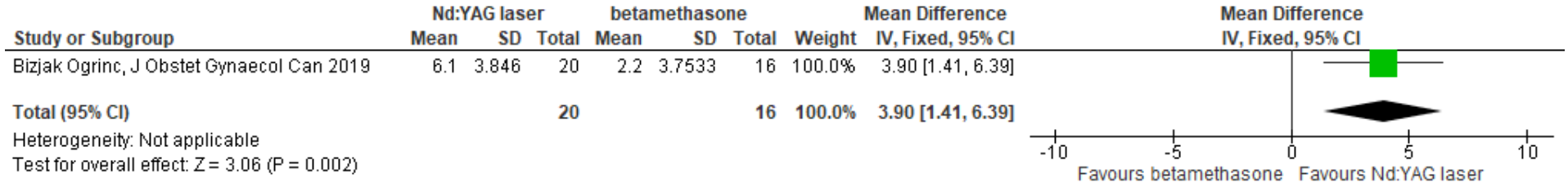
- **(New) VAS pain decrease from baseline (improvement of symptoms) (1 month)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	6.1	3.6324	20	1.8	3.5656	16	100.0%	4.30 [1.94, 6.66]
Total (95% CI)			**20**			**16**	**100.0%**	**4.30 [1.94, 6.66]**

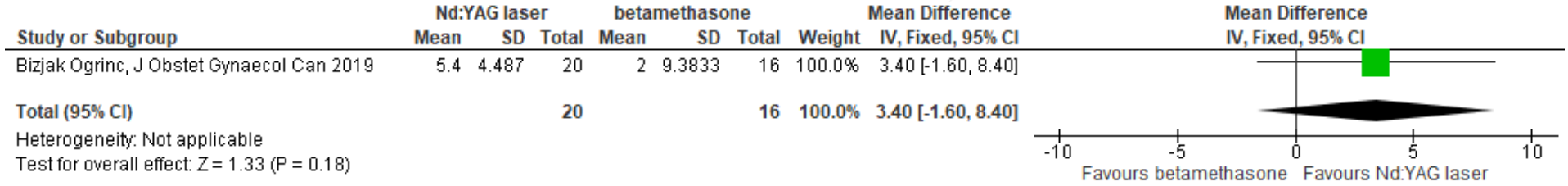
Heterogeneity: Not applicable
Test for overall effect: Z = 3.57 (P = 0.0004)



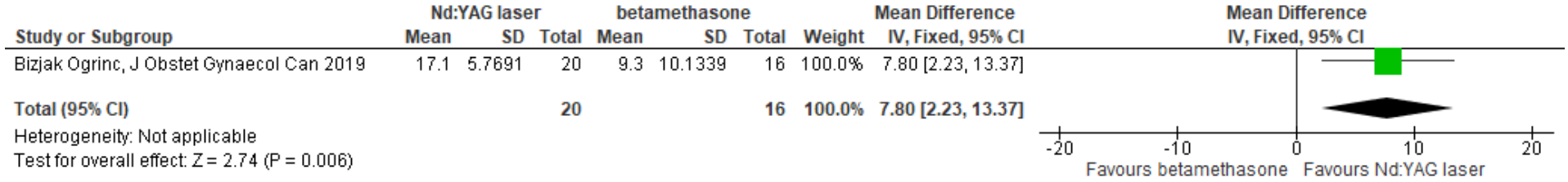
- **(New) VAS pain decrease from baseline (improvement of symptoms) (3 months)**



- **(New) VAS pain decrease from baseline (improvement of symptoms) (6 months)**



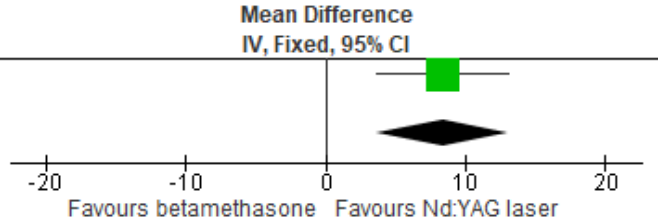
- **(New) Sum Score (itching, burning, pain) decrease from baseline (improvement of symptoms) (1 month)**



- **(New) Sum Score (itching, burning, pain) decrease from baseline (improvement of symptoms) (3 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	17.5	6.4101	20	9.1	7.6943	16	100.0%	8.40 [3.70, 13.10]
Total (95% CI)			**20**			**16**	**100.0%**	**8.40 [3.70, 13.10]**

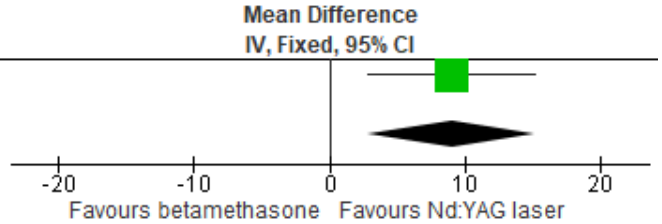
Heterogeneity: Not applicable
Test for overall effect: Z = 3.50 (P = 0.0005)



- **(New) Sum Score (itching, burning, pain) decrease from baseline (improvement of symptoms) (6 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	14.7	8.9741	20	5.7	9.571	16	100.0%	9.00 [2.88, 15.12]
Total (95% CI)			**20**			**16**	**100.0%**	**9.00 [2.88, 15.12]**

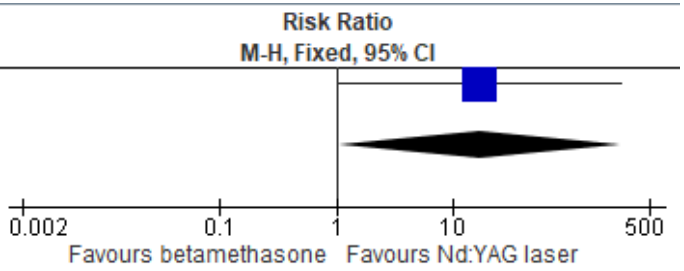
Heterogeneity: Not applicable
Test for overall effect: Z = 2.88 (P = 0.004)



- **(New) Sum score = 0 (itching, burning, pain) (improvement of symptoms) (3 months)**

Study or Subgroup	Nd:YAG laser Events	Total	betamethasone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	8	20	0	20	100.0%	17.00 [1.05, 276.03]
Total (95% CI)		**20**		**20**	**100.0%**	**17.00 [1.05, 276.03]**
Total events	8		0			

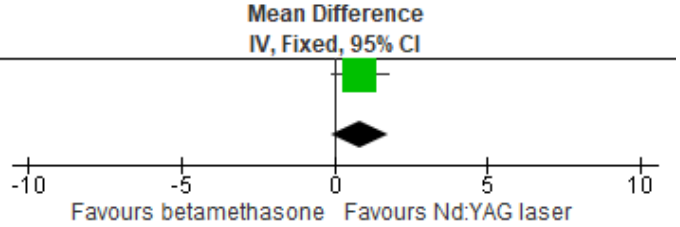
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)



- **(New) mean improvement score (0=no improvement - 3=complete improvement) (physician global assessment (6 months)**

Study or Subgroup	Nd:YAG laser Mean	SD	Total	betamethasone Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	0.58	1.25	20	-0.27	1.27	11	100.0%	0.85 [-0.08, 1.78]
Total (95% CI)			**20**			**11**	**100.0%**	**0.85 [-0.08, 1.78]**

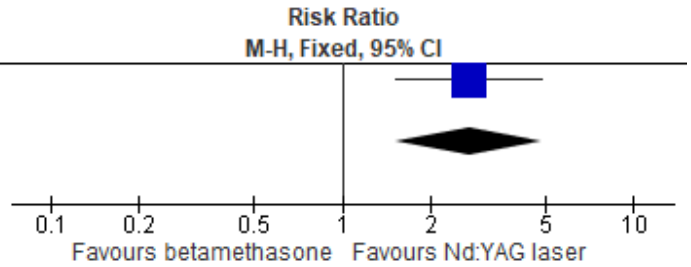
Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



- **(New) satisfaction - very satisfied or satisfied (patient global assessment) (3 months)**

Study or Subgroup	Nd:YAG laser Events	Total	betamethasone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bizjak Ogrinc, J Obstet Gynaecol Can 2019	20	20	7	20	100.0%	2.73 [1.53, 4.87]
Total (95% CI)		**20**		**20**	**100.0%**	**2.73 [1.53, 4.87]**
Total events	20		7			

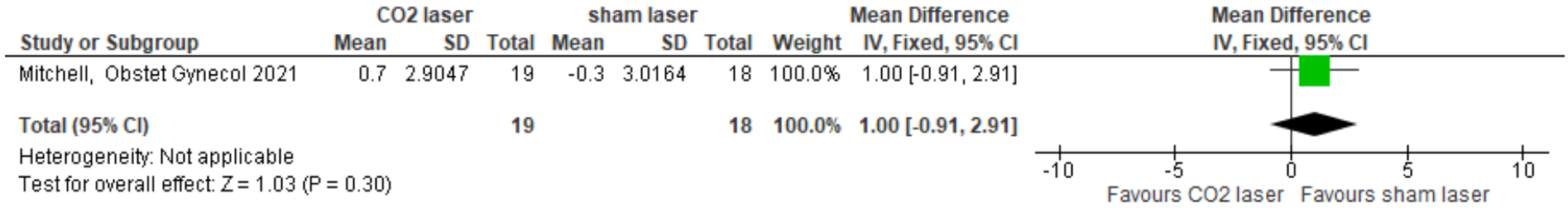
Heterogeneity: Not applicable
Test for overall effect: Z = 3.41 (P = 0.0006)



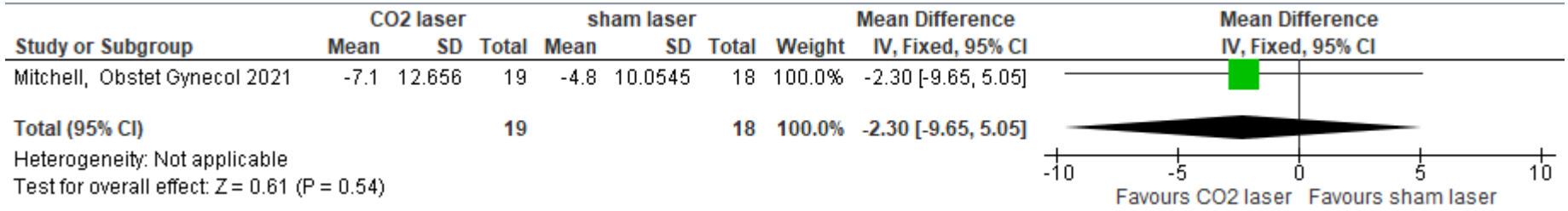
Laser vs. placebo

CO2 laser vs. sham laser

- **(New) Providers' Clinical Scoring System for Vulval Lichen Sclerosus – CSS mean change from baseline (physician global assessment) (6 months)**



- **(New) Patients' Clinical Scoring System for Vulval Lichen Sclerosus – CSS (mean change from baseline) (6 months)**

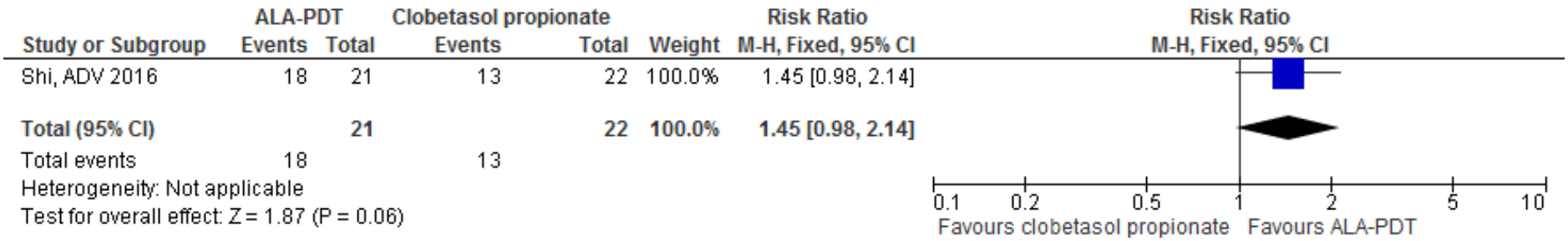


Photodynamic therapy vs. topical

Photodynamic therapy vs. ultrapotent TCS

ALA-PDT vs. clobetasol propionate 0.05% ointment

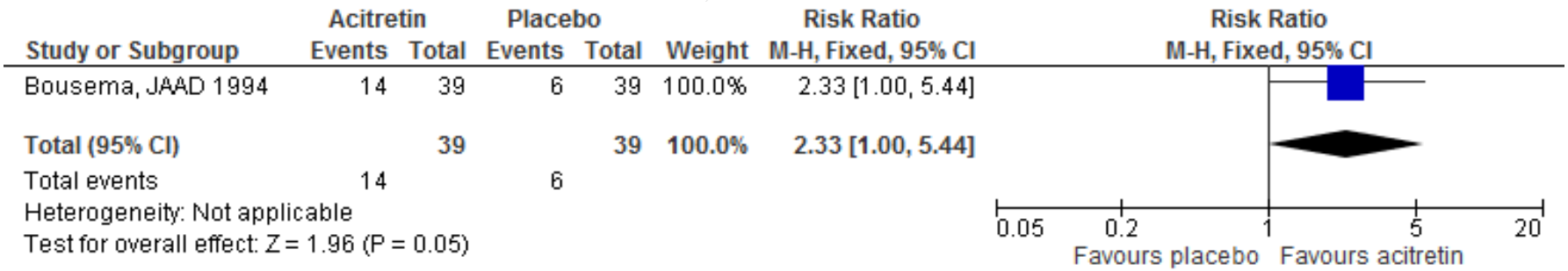
- **Complete and partial response (improvement of symptoms) (8 weeks)**



Systemic treatment vs. placebo

Acitretin p.o. vs. placebo

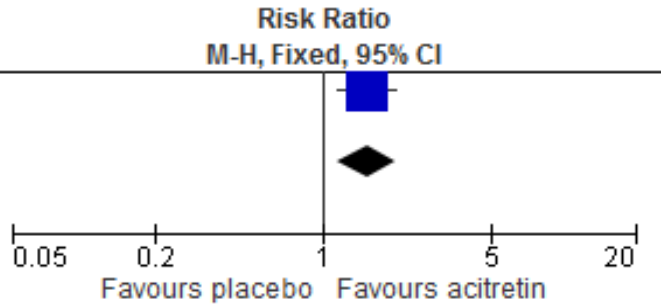
- **Responders (a patient who showed a decrease of at least two grades in one of the symptoms (pruritus or burning), without any worsening in any other symptom, a decrease of at least one grade in two of the signs (atrophy, hyperkeratosis, and secondary features) without any worsening in the other sign, and no increase in the extent of the lesions) (16 weeks)**



- **Partially or completely satisfied (patient global assessment) (16 weeks)**

Study or Subgroup	Acitretin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bousema, JAAD 1994	35	39	23	39	100.0%	1.52 [1.15, 2.02]
Total (95% CI)		**39**		**39**	**100.0%**	**1.52 [1.15, 2.02]**
Total events	35		23			

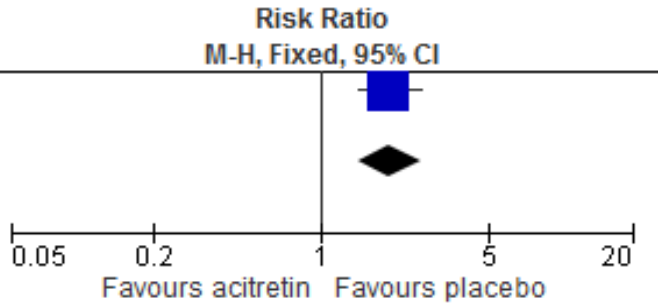
Heterogeneity: Not applicable
Test for overall effect: Z = 2.91 (P = 0.004)



- **Minor adverse events (16 weeks)**

Study or Subgroup	Acitretin Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bousema, JAAD 1994	39	39	20	39	100.0%	1.93 [1.42, 2.61]
Total (95% CI)		**39**		**39**	**100.0%**	**1.93 [1.42, 2.61]**
Total events	39		20			

Heterogeneity: Not applicable
Test for overall effect: Z = 4.23 (P < 0.0001)



b. Girls

No data

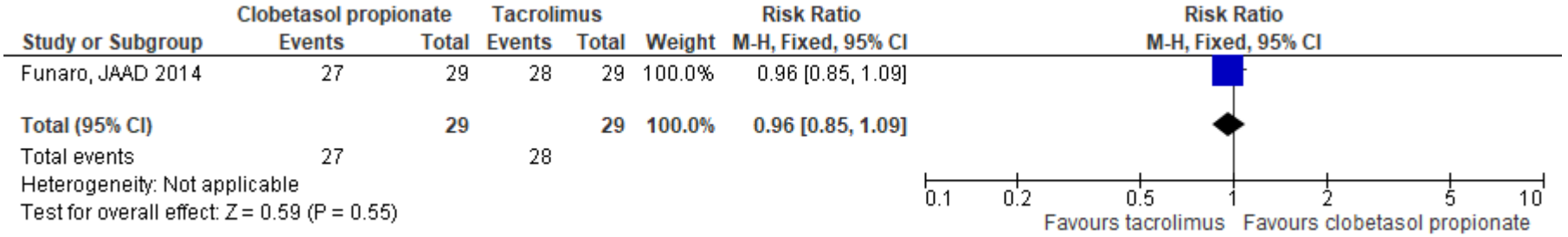
c. Women and girls

Topical vs. topical

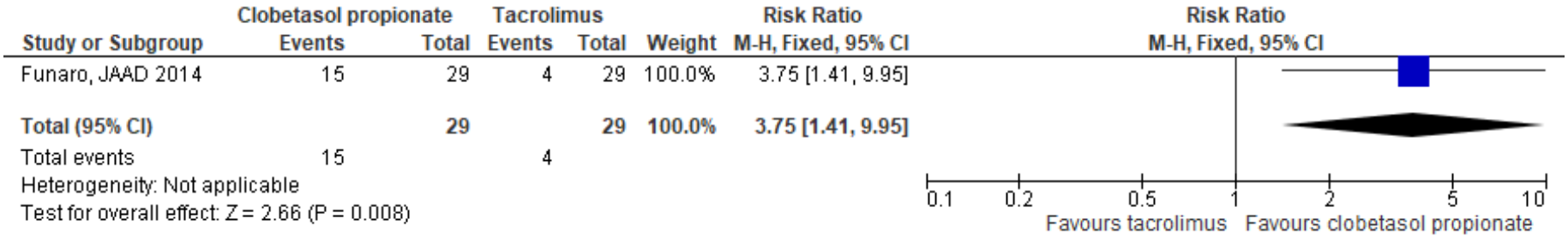
Ultrapotent TCS vs. TCI

Clobetasol propionate ointment vs. tacrolimus 0,1% ointment

- **Decrease in symptoms and signs of LS (improvement of symptoms) (3 months)**



- **No clinical signs or any reported symptoms at end of study (improvement of symptoms) (3 months)**

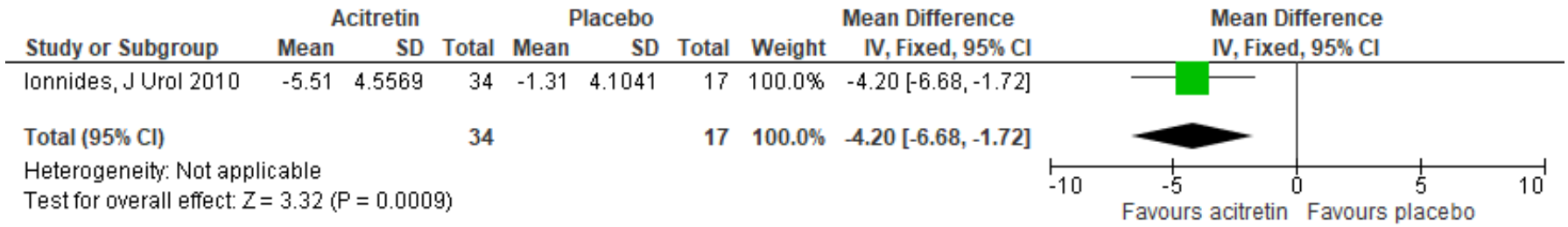


d. Men

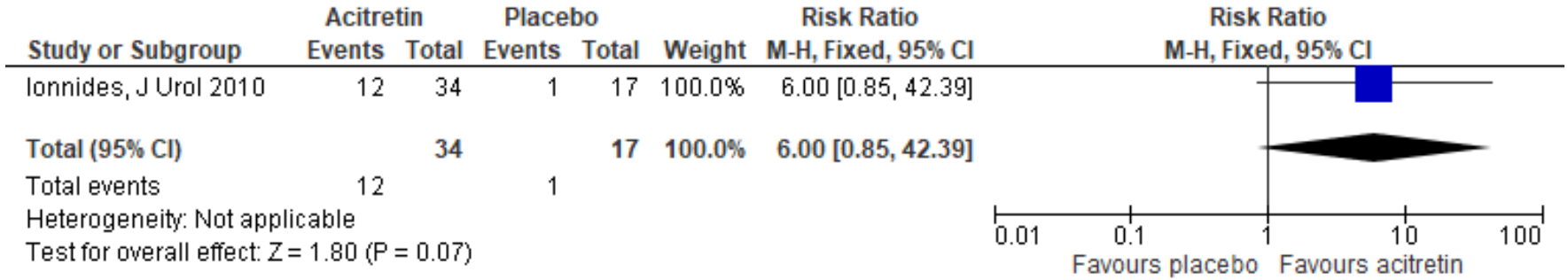
Systemic treatment vs. placebo

Acitretin vs. placebo

- **Improvement in DLQI mean change from baseline (quality of life) (20 weeks)**



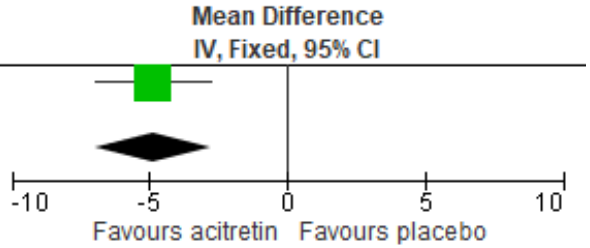
- **Complete response (improvement of symptoms) (20 weeks)**



- **Reduction in total clinical score (TCS) mean change from baseline (physician global assessment) (20 weeks)**

Study or Subgroup	Acitretin Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ionnides, J Urol 2010	-4.84	4.0385	34	0.06	3.3706	17	100.0%	-4.90 [-7.00, -2.80]
Total (95% CI)			**34**			**17**	**100.0%**	**-4.90 [-7.00, -2.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.57 (P < 0.00001)



e. Boys

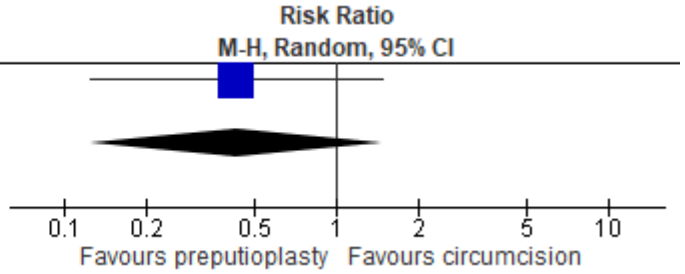
[Surgery vs. surgery]

Circumcision vs. preputioplasty and intralesional triamcinolone (PIT)

- **(New) Satisfaction (very satisfied or satisfied) with treatment (patient global assessment) (1 year)**

Study or Subgroup	Circumcision Events	Total	Preputioplasty Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lansdale, BJU Int 2021	2	7	8	12	100.0%	0.43 [0.12, 1.48]
Total (95% CI)		**7**		**12**	**100.0%**	**0.43 [0.12, 1.48]**
Total events	2		8			

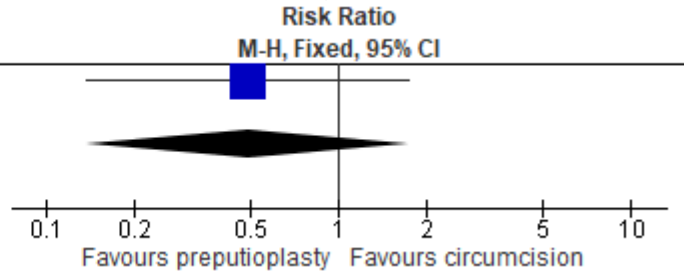
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)



- **(New) Satisfaction (very satisfied or satisfied) with cosmetic outcome (patient global assessment) (1 year)**

Study or Subgroup	circumcision Events	Total	preputioplasty Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lansdale, BJU Int 2021	2	7	7	12	100.0%	0.49 [0.14, 1.74]
Total (95% CI)		**7**		**12**	**100.0%**	**0.49 [0.14, 1.74]**
Total events	2		7			

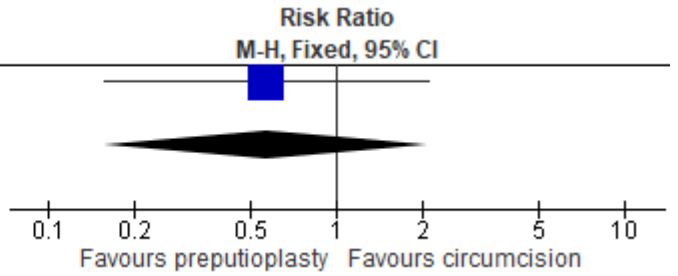
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.27)



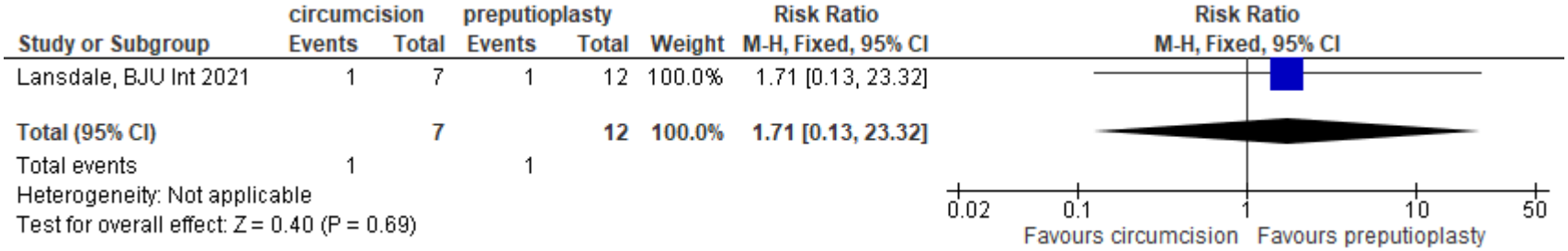
- **(New) Satisfaction (very satisfied or satisfied) with treatment of symptoms (patient global assessment) (1 year)**

Study or Subgroup	circumcision Events	Total	preputioplasty Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lansdale, BJU Int 2021	2	7	6	12	100.0%	0.57 [0.16, 2.10]
Total (95% CI)		**7**		**12**	**100.0%**	**0.57 [0.16, 2.10]**
Total events	2		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.84 (P = 0.40)



- **(New) Patients with minor adverse events (1 year)**



f. Men and boys

No data

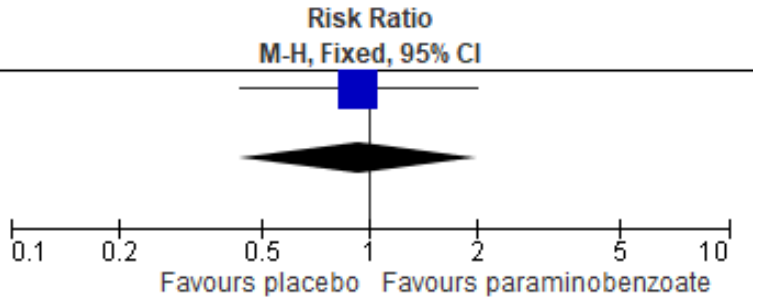
g. Mixed (adults)

Paraminobenzoate vs. placebo

- **Improvement of symptoms (2 months)**

Study or Subgroup	Paraminobenzote Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Buxton, JDT 1990	6	12	7	13	100.0%	0.93 [0.44, 1.98]
Total (95% CI)		**12**		**13**	**100.0%**	**0.93 [0.44, 1.98]**
Total events	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.19 (P = 0.85)

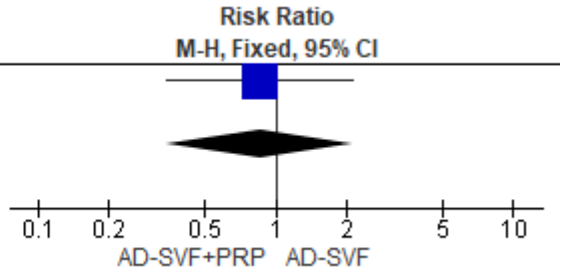


Adipose tissue derived-stromal vascular fraction (AD-SVF) vs. adipose tissue derived-stromal vascular fraction (AD-SVF) + PRP

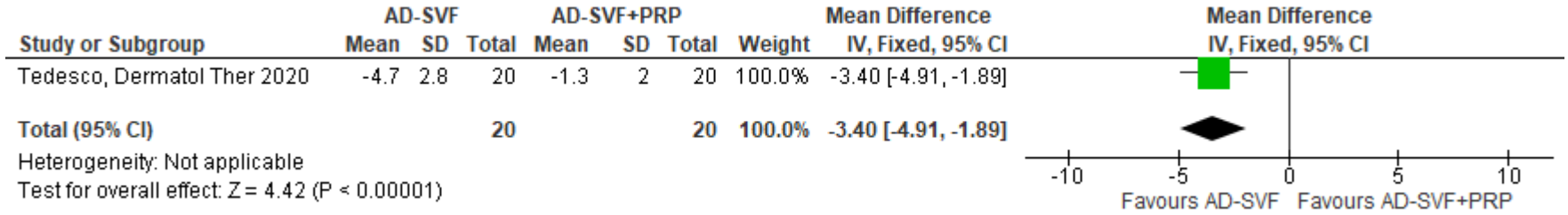
- **(New) Clinical score = 3 - progressive decrease in symptoms until they disappeared (improvement of symptoms) (6 months)**

Study or Subgroup	AD-SVF Events	Total	AD-SVF+PRP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tedesco, Dermatol Ther 2020	6	20	7	20	100.0%	0.86 [0.35, 2.10]
Total (95% CI)		**20**		**20**	**100.0%**	**0.86 [0.35, 2.10]**
Total events	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.34 (P = 0.74)



- **(New) DLQI mean difference from baseline (quality of life) (6 months)**



h. Mixed (children)

No data

i. Mixed (adults and children)

No data

3. Appendix B: GRADE evidence tables

a. Women

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
Improvement of symptoms: (clinical resolution): clobetasol propionate vs. mometasone furoate (12 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious[a]	none	24/27 (88.9%)	88.9%	**RR 1.00** (0.83 to 1.21)	0 fewer per 1,000 (from 151 fewer to 187 more)	⊕⊕⊕⊕ High	Critical
Improvement of symptoms: (GOS 75) clobetasol propionate vs. mometasone furoate (12 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	10/27 (37.0%)	48.2%	**RR 0.77** (0.41 to 1.44)	111 fewer per 1,000 (from 284 fewer to 212 more)	⊕⊕◯◯ Low	Critical
Improvement of symptoms: (GSS 75) clobetasol propionate vs. mometasone furoate (12 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	16/27 (59.3%)	66.7%	**RR 0.89** (0.59 to 1.34)	73 fewer per 1,000 (from 273 fewer to 227 more)	⊕⊕◯◯ Low	Critical
Improvement of symptoms: (complete response): clobetasol propionate vs. testosterone (3 months follow up)												
1	observational studies	very serious[c]	not serious	not serious	serious[b]	none	13/20 (65.0%)	30.0%	**RR 2.17** (1.03 to 4.55)	351 more per 1,000 (from 9 more to 1,000 more)	⊕◯◯◯ Very low	Critical
Improvement of symptoms: (complete & incomplete response): clobetasol propionate vs. testosterone (1 year follow up)												
1	observational studies	very serious[c]	not serious	not serious	not serious	none	18/20 (90.0%)	40.0%	**RR 2.25** (1.29 to 3.92)	500 more per 1,000 (from 116 more to 1,000 more)	⊕◯◯◯ Very low	Critical
Improvement of symptoms: (responders): mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	27/32 (84.4%)	78.1%	**RR 1.08** (0.85 to 1.37)	62 more per 1,000 (from 117 fewer to 289 more)	⊕⊕⊕◯ Moderate	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
Improvement of symptoms: (GOS 75) mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	15/32 (46.9%)	28.1%	**RR 1.67** (0.86 to 3.24)	188 more per 1,000 (from 39 fewer to 629 more)	⊕⊕⊕◯ Moderate	Critical
Improvement of symptoms: (GSS 75) mometasone furoate (tapering) vs. mometasone furoate (continuous) (3 months)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	22/32 (68.8%)	62.5%	**RR 1.10** (0.77 to 1.57)	63 more per 1,000 (from 144 fewer to 356 more)	⊕⊕⊕◯ Moderate	Critical
Improvement of symptoms: (itching): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	15	15	-	MD **2.5 lower** (5.69 lower to 0.69 higher)	⊕⊕◯◯ Low	Critical
Improvement of symptoms: (burning/pain): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	15	15	-	MD **1 lower** (4.1 lower to 2.1 higher)	⊕◯◯◯ Very low	Critical
Physician global assessment: (total clinicians score): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	15	15	-	MD **0.5 lower** (4.03 lower to 3.03 higher)	⊕◯◯◯ Very low	Important
QoL: (Skindex-29 score): UVA-1 vs. clobetasol (mean decrase from baseline at 3 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	15	15	-	MD **24.7 lower** (50.17 lower to 0.77 higher)	⊕⊕◯◯ Low	Important
Improvement of symptoms: (complete and partial response): ALA-PDT vs. clobetasol propionate (8 weeks)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	18/21 (85.7%)	59.1%	**RR 1.45** (0.98 to 2.14)	266 more per 1,000 (from 12 fewer to 674 more)	⊕⊕◯◯ Low	Critical
Improvement of symptoms: (responders): acitretin vs. placebo (16 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[b]	none	14/39 (35.9%)	15.4%	**RR 2.33** (1.00 to 5.44)	205 more per 1,000 (from 0 fewer to 684 more)	⊕⊕⊕◯ Moderate	Critical
Patient global assessment: (partially or completely satisfied): acitretin vs. placebo (16 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	35/39 (89.7%)	59.0%	**RR 1.52** (1.15 to 2.02)	307 more per 1,000 (from 88 more to 602 more)	⊕⊕⊕◯ Moderate	Important
Minor adverse events: acitretin vs. placebo (16 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	39/39 (100.0%)	51.3%	**RR 1.93** (1.42 to 2.61)	477 more per 1,000 (from 215 more to 826 more)	⊕⊕⊕⊕ High	Important
New: Physician global assessment: (Providers' CSS): CO2 laser vs. sham laser (mean change from baseline at 6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	19	18	-	MD **1 higher** (0.91 lower to 2.91 higher)	⊕⊕◯◯ Low	Important
New: Patient global assessment: (Patients' CSS): CO2 laser vs. sham laser (mean change from baseline at 6 months)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	19	18	-	MD **2.3 lower** (9.65 lower to 5.05 higher)	⊕◯◯◯ Very low	Important
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **1.2 higher** (1.42 lower to 3.82 higher)	⊕◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **1.4 higher** (1.16 lower to 3.96 higher)	⊕◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS burning decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **2.7 higher** (0.35 higher to 5.05 higher)	⊕◯◯◯ Very low	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **2.3 higher** (0.39 lower to 4.99 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **3 higher** (0.69 higher to 5.31 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS itching decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **1.9 higher** (2.7 lower to 6.5 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)												
1	randomised trials	very serious[c]	not serious	not serious	not serious	none	20	16	-	MD **4.3 higher** (1.94 higher to 6.66 higher)	⨁⨁◯◯ Low	Critical
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **3.9 higher** (1.41 higher to 6.39 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (VAS pain decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **3.4 higher** (1.6 lower to 8.4 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 1 month)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **7.8 higher** (2.23 higher to 13.37 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 3 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **8.4 higher** (3.7 higher to 13.1 higher)	⊕◯◯◯ Very low	Critical
New: Improvement of symptoms: (sum score decrease): Nd:YAG laser vs. betamethasone (mean change from baseline at 6 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **9 higher** (2.88 higher to 15.12 higher)	⊕◯◯◯ Very low	Critical
New: Improvement of symptoms: (sum score = 0): Nd:YAG laser vs. betamethasone (3 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	8/20 (40.0%)	0/20 (0.0%)	**RR 17.00** (1.05 to 276.03)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	Critical
New: Physician global assessment: (mean improvement score): Nd:YAG laser vs. betamethasone (6 months)												
1	randomised trials	very serious[c]	not serious	not serious	serious[b]	none	20	16	-	MD **0.85 higher** (0.02 higher to 1.68 higher)	⊕◯◯◯ Very low	Important
New: Patient global assessment: (very satisfied or satisfied): Nd:YAG laser vs. betamethason (3 months)												
1	randomised trials	very serious[c]	not serious	not serious	not serious[b]	none	20/20 (100.0%)	7/20 (35.0%)	**RR 2.79** (1.93 to 2.85)	627 more per 1,000 (from 325 more to 648 more)	⊕⊕◯◯ Low	Important
New: Improvement of symptoms (VAS itching): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **1.43 lower** (3.22 lower to 0.36 higher)	⊕⊕◯◯ Low	Critical
New: Improvement of symptoms: (VAS burning): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **1.78 lower** (3.69 lower to 0.13 higher)	⊕⊕◯◯ Low	Critical
New: Improvement of symptoms: (VAS irritation or tearing): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **2.83 lower** (4.73 lower to 0.93 lower)	⊕⊕◯◯ Low	Critical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
New: Improvement of symptoms: (VAS tearing of vulval skin): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **0.45 lower** (2.56 lower to 1.66 higher)	⨁⨁◯◯ Low	Critical
New: Improvement of symptoms: (VAS painful defecation): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	27	24	-	MD **0.11 lower** (1.62 lower to 1.4 higher)	⨁◯◯◯ Very low	Critical
New: Improvement of symptoms: (VSQ): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **3.34 lower** (5.91 lower to 0.77 lower)	⨁⨁◯◯ Low	Critical
New: Improvement of symptoms: (VHI): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **2.35 higher** (0.16 higher to 4.54 higher)	⨁⨁◯◯ Low	Critical
New: Patient global assessment (PGI-I better or much better): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	23/27 (85.2%)	13/25 (52.0%)	**RR 1.64** (1.09 to 2.46)	333 more per 1,000 (from 47 more to 759 more)	⨁⨁◯◯ Low	Important
New: Patient global assessment: (PGI-S satisfied or very satisfied): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	21/27 (77.8%)	9/25 (36.0%)	**RR 2.16** (1.23 to 3.78)	418 more per 1,000 (from 83 more to 1,000 more)	⨁⨁◯◯ Low	Important
New: QoL: (Skindex-29): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	not serious[b]	none	27	24	-	MD **10.91 lower** (18.12 lower to 3.7 lower)	⨁⨁⨁◯ Moderate	Critical
New: Sexual function: (VAS pain with sex): CO2 laser vs. clobetasol propionate (6 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women		Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[c]	not serious	not serious	Very serious[b]	none	27	24	-	MD **0.55 lower** (1.79 lower to 0.69 higher)	⨁◯◯◯ Very low	Critical
New: Urinary function: (VAS dysuria): CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	serious[b]	none	27	24	-	MD **1.33 lower** (2.95 lower to 0.29 higher)	⨁⨁◯◯ Low	Critical
New: Patients with minor adverse events: CO2 laser vs. clobetasol propionate (6 months)												
1	randomised trials	serious[c]	not serious	not serious	very serious[b]	none	1/27 (3.7%)	1/24 (4.2%)	**RR 0.89** (0.06 to 13.45)	5 fewer per 1,000 (from 39 fewer to 519 more)	⨁◯◯◯ Very low	Important

a. No clinical important difference - CI was between MIDs
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs
c. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias

b. Girls

No data

c. Women and girls

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women and girls		Relative (95% CI)	Absolute (95% CI)		
Improvement of symptoms: clobetasol propionate vs. tacrolimus (3 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	27/29 (93.1%)	96.6%	**RR 0.96** (0.85 to 1.09)	39 fewer per 1,000 (from 145 fewer to 87 more)	⨁⨁⨁◯ Moderate	Critical
Improvement of symptoms: (absence of symptoms): clobetasol propionate vs. tacrolimus (2 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Women and girls		Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	not serious	none	15/29 (51.7%)	13.8%	**RR 3.75** (1.41 to 9.95)	380 more per 1,000 (from 57 more to 1,000 more)	⨁⨁⨁◯ Moderate	Critical

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. No clinical important difference - CI was between MIDs

d. Men

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Men		Relative (95% CI)	Absolute (95% CI)		
QoL (DLQI): acitretin vs. placebo (mean change from baseline at 20 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	34	17	-	MD **4.2 lower** (6.68 lower to 1.72 lower)	⨁⨁⨁◯ Moderate	Critical
Improvement of symptoms: (complete response): acitretin vs. placebo (20 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	12/34 (35.3%)	5.9%	**RR 6.00** (0.85 to 42.39)	295 more per 1,000 (from 9 fewer to 1,000 more)	⨁⨁⨁◯ Moderate	Critical
Physician global assessment (total clinical score): acitretin vs. placebo (mean change from baseline at 20 weeks)												
1	randomised trials	not serious	not serious	not serious	not serious	none	34	17	-	MD **4.9 lower** (7 lower to 2.8 lower)	⨁⨁⨁⨁ High	Important

a. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

e. Boys

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Boys		Relative (95% CI)	Absolute (95% CI)		
New: Patient global assessment: (very satisfied or satisfied with treatment): circumcision vs. PIT (1 year)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/7 (28.6%)	8/12 (66.7%)	**RR 0.43** (0.12 to 1.48)	380 fewer per 1,000 (from 587 fewer to 320 more)	⨁◯◯◯ Very low	Important
New: Patient global assessment: (very satisfied or satisfied with cosmetic outcome): circumcision vs. PIT (1 year)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/7 (28.6%)	7/12 (58.3%)	**RR 0.49** (0.14 to 1.74)	298 fewer per 1,000 (from 502 fewer to 432 more)	⨁◯◯◯ Very low	Important
New: Patient global assessment: (very satisfied or satisfied with treatment of symptoms): circumcision vs. PIT (1 year)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	2/7 (28.6%)	6/12 (50.0%)	**RR 0.57** (0.16 to 2.10)	215 fewer per 1,000 (from 420 fewer to 550 more)	⨁◯◯◯ Very low	Important
New: Patients with minor adverse events: circumcision vs. PIT (1 year)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	1/7 (14.3%)	1/12 (8.3%)	**RR 1.71** (0.13 to 23.32)	59 more per 1,000 (from 73 fewer to 1,000 more)	⨁◯◯◯ Very low	Important

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

f. Men and boys

No data

g. Mixed (adults)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Men and boys		Relative (95% CI)	Absolute (95% CI)		
Improvement of symptoms (marked, moderate or slight improvement) paraminobenzote vs. placebo (2 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	6/12 (50.0%)	53.9%	**RR 0.93** (0.44 to 1.98)	38 fewer per 1,000 (from 302 fewer to 528 more)	⊕◯◯◯ Very low	Critical
New: Improvement of symptoms (progressive decrease in symptoms until they disappeared): AD-SVF vs. AD-SVF+PRP (6 months)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	6/20 (30.0%)	7/20 (35.0%)	**RR 0.86** (0.35 to 2.10)	49 fewer per 1,000 (from 227 fewer to 385 more)	⊕◯◯◯ Very low	Critical
New: QoL (DLQI): AD-SVF vs. AD-SVF+PRP (6 months)												
1	randomised trials	very serious[a]	not serious	not serious	not serious	none	20	20	-	MD **3.4 lower** (4.91 lower to 1.89 lower)	⊕⊕◯◯ Low	Critical

a. Downgraded by one increment if the majority of the evidence was at high risk of bias, and downgraded by two increments if the majority of the evidence was at very high risk of bias
b. Downgraded by one increment if the confidence interval crossed one MID or by two increments if the confidence interval crossed both MIDs

h. Mixed (children)

No data

i. Mixed (adults and children)

No data

4. Appendix C: Non-comparative or non-prospective trials

a. Women and girls with genital disease

Title	First author + year	Journal	Study design	Study population	Intervention	Follow up	Outcome	Notes
Age 0-12 years								
TCS								
New: Characteristics Among Premenarchal Girls With Lichen Sclerosus	Wang 2021	J. Low. Genit. Tract Dis.	Retrospective chart review	19 prepubertal females wit VLS age: 3.3-13.3	TCS regimen: 4 w clobetasol propionate, then 2 w triamcinolone acetonide	No information (4 year study period)	LS symptoms (n =19) Resolution/improvement: 14/19 (73.7%) Relapse 3/19 (15.8%) Unknown 2/19 (10.5%) LUTS symptoms (n=12 at time of LS diagnosis): Resolution/improvement 7/12 (58.3%) Unchanged symptoms 3/12 (25.0%) Unknown 2/12 (16.7%) among others	
A retrospective analysis of paediatric patients with lichen sclerosus treated with a standard protocol of class I topical corticosteroid and topical calcineurin inhibitor	Anderson 2016	J Dermatolog Treat	Retrospective	14 girls age 2-10	Clobetasol propionate twice daily bridging to 0.1% tacrolimus with steroid reduced to twice daily at weekends and then replaced with tacrolimus	No information	93% complete clearance (mean 43.1 w, range 4 to 156 w)	Regimen not identical for every patient
Childhood lichen sclerosus: a long-term follow-up	Patrizi 2010	Pediatr Dermatol	Retrospective	15 girls age: 4-11	Clobetasol propionate nightly with tapered regimen after remission	M 4.7 y	Remission was obtained in all patients after 2–16 w; relapses in nine patients (60%) after approximately 1 y	
Clobetasol propionate in the treatment of premenarchal vulvar lichen sclerosus	Smith 2001	Obstet Gynecol	Retrospective chart review	15 girls age: 3-11	Clobetasol propionate 2-4 weeks then tapered to a less potent steroid	At least 1y	Good improvement in symptoms and skin appearance within 4–7 weeks in 14 girls (93%); at least 1 year of follow-up by clinic visit or telephone interview was available in 11 girls. Of these 11 girls, 2 had no further vulval symptoms after the initial treatment, 5 had one or two total flares, 3 reported three to eight flares per year, and 1 girl continues to be unresponsive to therapy	
Ultrapotent topical corticosteroid treatment of childhood genital lichen sclerosus	Garzon 1999	Arch Dermatol	Retrospective	10 girls age: 2.5-11.5	Ultrapotent TCS ointment with 0.05% clobetasol, 0.05% diflorasone diacetate, 0.05% betamethasone dipropionate, or betamethasone dipropionate without propylene glycol twice daily for 6 w	6 m-3 y	All children demonstrated clinical improvement, 6 clear after six weeks, remaining 4 showed further improvements after additional two weeks of therapy	
Treatment of childhood vulvar lichen sclerosus with potent topical corticosteroid	Fischer 1997	Pediatr Dermatol		11 girls age: 3-11	Betamethasone dipropionate 0.05% 3 times a day for 3 w then twice a day	3 m - 3 y	Excellent response to therapy in all cases; 8 out of 11 experienced complete remission after 3 m of therapy	
Topical calcineurin inhibitors								
New: Tacrolimus 0.03% ointment for treatment of paediatric lichen sclerosus: a case series and literature review	Mazzilli 2018	Int. J. Med. Res.	Case series	10 girls age 4-9 with VLS	Tacrolimus 0.03% ointment twice a day for 6 weeks	6 weeks of treatment and 6 weeks of follow-up	Itching and burning completely disappeared after 2 weeks in all patients; skin lesions were in remission at 1 week after beginning treatment, with residual milia in all patients no adverse events were recorded	very little information on outcomes
Low-concentration topical tacrolimus for the treatment of anogenital lichen sclerosus in childhood: maintenance treatment to reduce recurrence	Li 2013	J Pediatr Adolesc Gynecol		14 girls age 4-11	Topical 0.03% tacrolimus twice daily for 16 weeks and then twice weekly for 6 months	12 m	Complete response in 5, 9 and 11 at week 8, week 16 and month 10 respectively. 4 of 5 who stopped treatment at 16 weeks had a recurrence of symptoms. 2 of 9 who continued twice weekly treatment had recurrent symptoms	
Age 13-17 years								
Age 18+								
Emollients								
New: Effects of a topical ointment on responses to treatments used for common genital diseases and on quality of life	de Belilovsky 2020	Cogent Medicine	Cohort study	26 women with LS	Topical emollient in addition to their standard therapy	M 60 days	Pruritus: 0.72 ±1.65 (-77,71%) burning sensations: 0.38±0.94 (-89,24%) dyspareunia: 0.96±2.29 (-50%) discomfort: 0.73±1.31 (-81%) dryness sensation: 0.58±0.95 (-87.07%) spontaneous pain: 0.07±0.39 (-87.5%)	

							global symptoms score: 3.42±3.92 (-80.61%) mGSS75: 20/26 mGSS50: 22/26 Global Clinical Score: 4.69±2.71 (-59.2) mGCS75: 6/26 mGCS50: 17/26 IGA ≥2: 19/26 among others	
TCS								
New: Assessing patient satisfaction and compliance with compounded clobetasol propionate 0.05% and estradiol 0.01% for the management of lichen sclerosus with coexisting genitourinary syndrome of menopause	Racher 2017	J Low Genit Tract Dis	Cohort study	17 females with VLS and coexisting genitourinary syndrome of menopause; (14 of the 17 subjects completed a short survey)	Clobetasol propionate and estradiol 0.01% in an emollient base	no information	Very satisfied: 85.7% more satisfied than with previous treatment: 92.9%	Conference abstract with little information; no information on previous treatment or treatment duration
Lichen sclerosus. Therapy with clobetasol propionate	Lorenz 1998	J Reprod Med	Retrospective chart review	81 females with symptomatic, biopsy proven VLS	Clobetasol proprionate "standard regimen"	3 m	77%: complete remission of symptoms 18%: partial remission 5%: no change	
The treatment of vulval lichen sclerosus with a very potent topical steroid (clobetasol propionate 0.05%) cream	Dalziel 1991	Br J Dermatol	Prospective	15 females with VLS	Clobetasol proprionate cream twice daily for 12 weeks	12 w	Marked clinical improvement in the 13 patients who completed the study	
Vulvar lichen sclerosus: effect of long-term topical application of a potent steroid on the course of the disease	Renaud-Vilmer 2004	Arch Dermatol	Prospective	83 females	Clobetasol proprionate once daily for 4 w and then twice weekly for another 4 w in combination with a moisturizing cream that was continued as maintenance therapy	M 4.7 y	Complete remission in 45 patients (54%)	
The efficacy of clobetasol 0.05% for treatment of vulvar lichen sclerosus	Schwarz 2008	Geburtshilfe Frauenheilkd	Retrospective	96 females with biopsy proven VLS	Clobetasol proprionate for at least 12 weeks	at least 3 m	Overall response rate was 59.7 % improvement of symptoms: 70.9%	
Health-related quality of life and patient-defined benefit of clobetasol 0.05% in women with chronic lichen sclerosus of the vulva	Schwegler 2011	Dermatology	Retrospective	96 females	Clobetasol proprionate twice daily in the first m and once daily during the second and third m	at least 3 m	Overall response rate was 59.2% global PBI score was 3.06	
Vulvar lichen sclerosus in postmenopausal women: a comparative study for treating advanced disease with clobetasol propionate 0.05%	Diakomanolis 2002	Eur J Gynaecol Oncol	Prospective	54 postmenopausal females with VLS	Clobetasol proprionate Group 1: 3 m than as required Group 2: 6 m	12 m	Complete response 6 m: group 1: 59%; group 2: 85% complete response 12 m: group 1: 48%; group 2: 74%.	

Vulvar lichen sclerosus: a comparison of the short-term topical application of clobetasol dipropionate 0.05% versus mometasone furoate 0.1%	Murina 2015	J Low Genit Tract Dis	Retrospective comparative case series	96 females	Group 1 n=47: Clobetasol proprionate Group 2 n=49: MMF for 8 w	12 m	Responders group 1: 73% responders group 2: 81,6%	
Clobetasol propionate vs. mometasone furoate in 1-year proactive maintenance therapy of vulvar lichen sclerosus: results from a comparative trial	Corazza 2016	J Eur Acad Dermatol Venereol	Prospective	48 females who had responded to therapy with either CP or MMF in an earlier 12-week trial randomized active treatment phase trial	Clobetasol proprionate n=24 or MMF n=24 twice weekly as long-term maintenance treatment	52 w	2/24 (8.33%) subjects among the CP patients and 1/24 (4.17%) among the MMF patients experienced a relapse, mean time to relapse 30 w	
New: Measuring perceived benefit and disease-related burden in patients affected with vulvar lichen sclerosus after a standard topical corticosteroid treatment. Results from a cohort study using Pictorial Representation of Illness and Self-measure and Dermatology Life Quality Index	Borghi 2020	Dermatologic Therapy.	Prospective, cohort study	63 women with a histologically proven LS	MMF ointment once daily for 5 d/w for 4 w, then on alternate days for 4 w and, for the third m, twice weekly	12 w	Median [1Q 3Q] Global Subjective Score (0-20): bl: 9 [5-14] w12: 2 [0-6] Dyspareunia (0-10): bl: 6.5 [0-10] w12: 1.5 [0-7] Global Objective Score (0-15): bl: 4 [3-6] w12: 2 [1-4] DLQI (0-30): bl: 6 [3-8] w12: 2 [1-5] PRISM (SIS 0-273 mm): bl: 85 [55-180] w12: 180 [90-270] among others	
New: Does longer duration of corticosteroid treatment improve clearance in vulvar lichen sclerosus? Results from a single centre, comparative, open label study	Corazza 2021	Dermatologic Therapy.	Retrospective, comparative cohort study	29 women (3 dropped out)	MMF ointment five consecutive days/week for 24 w	24 w	GSS = 0: 16/29 GOS = 0: 4/29 GSS and GOS = 0: 3/29 Median [IQR] MD GSS (0–20): −10 [−17-7] MD GOS (0.12): −3 [−4-2] MD dyspareunia (0-10): 0 [−70] GSS75: 18/29 D75: 4/29 GOS75: 13/29	New: Does longer duration of corticosteroid treatment improve clearance in vulvar lichen sclerosus? Results from a single centre, comparative, open label study
				32 women (4 dropped out)	MMF ointment five consecutive days/week for 12 w		GSS = 0: 15/32 GOS = 0: 6/32 GSS and GOS = 0: 5/32 Median [IQR] MD GSS (0–20):−9.5 [−14-5] MD GOS (0.12): −2[−4-1] MD dyspareunia (0-10): 0[−5 0] GSS75: 22/32 D75: 7/32 GOS75: 10/32	

New: Mometasone furoate in the treatment of vulvar lichen sclerosus: could its formulation influence efficacy, tolerability and adherence to treatment?	Corazza 2018	J. Dermatol. Treat.	Retrospective, comparative cohort study	27 women (2 dropped out)	MMF cream 5 d/w for 4 w, then on alternate days for 4 w and twice weekly during the third m	12 w	GSS75: 12/27 GOS75: 11/27 GSS50: 21/27 GOS50: 19/27 itching VAS: bl: 7.54±3.34 w12: 2.11±2.6 burning VAS: bl: 4.84±3.21 w12: 1.59±1.92 satisfaction with treatment: 22/27 convenience of treatment: 25/27 among others	
				37 women (1 dropped out)	MMF ointment 5 d/w for 4 w, then on alternate days for 4 w and twice weekly during the third m		GSS75: 25/37 GOS75: 17/37 GSS50: 30/37 GOS50: 30/37 itching VAS: bl 6.35±3.27 w12: 1.27±2.59 burning VAS: bl: 4.72±3.90 w12: 0.77±1.91 satisfaction with treatment: 31/37 convenience of treatment: 33/37 among others	
New: Topic treatment of vulvar lichen sclerosus: Symptoms control and risk of progression to malignancy	Sina 2019	Int J Gynecol Cancer	Retrospective cohort study	231 females with VLS	MMF ointment and emollient cream 30 d followed by a maintenance phase with emollient creams only at least twice a day	at least 1 y	Remission of symptoms: 65% required momethason after 30 days: 16% not effective: 19% vulvar carcinoma 24/144 VIN 4: 4/144	Neoplastic progression was evaluated in 144 patients; conference abstract with little information on outcomes
New: Combined therapy in vulvar lichen sclerosus: does topical tretinoin improve the efficacy of mometasone furoate?	Borghi 2017	J. Dermatolog. Treat.	Retrospective, nonrandomized, comparative cohort study	21 women; 3 drop out	MMF ointment plus tretinoin 0.05% cream 5 consecutive d/w for 12 w	12 w	Responders: 13/21* GSS75: 8/21* (2 patients were asymptomatic) GOS75: 11/21* GGS50: 12/21* (2 patients were asymptomatic) GOS50: 16/21* very satisfied 9/21* moderately satisfied 5/21* Adverse events reported: 6/18 among others	
				20 women; 1 drop out	MMF ointment plus a cold cream 5 consecutive d/w for 12 w		Responders: 15/20* GSS75: 15/20* (4 patients were asymptomatic) GOS75: 12/20* GGS50: 15/20* (4 patients were asymptomatic) GOS50: 19/20* very satisfied 13/20* moderately satisfied 4/20* Adverse events reported: 2/19 among others	

Topical mometasone furoate for vulvar lichen sclerosus	Cattaneo 2003	J Reprod Med	Cohort study	31 females with VLS	MMF once daily for 4 w and then twice weekly for 8 w	12 w	All the patients had a significant improvement in the gross aspects of the disease and a very dramatic decrease in symptoms	
Proactive maintenance therapy with a topical corticosteroid for vulvar lichen sclerosus: preliminary results of a randomized study	Virgili 2013	Br J Dermatol	Prospective	27 females	MMF once daily for 12 w	12 w	25 completely or almost completely healed after 12 w	Maintenance phase (52 w) were 25 healed patients were randomized to apply either mometasone furoate 0·1% ointment twice weekly, a cold cream once daily or topical vitamin E once daily.
Mometasone fuoroate 0.1% ointment in the treatment of vulvar lichen sclerosus: a study of efficacy and safety on a large cohort of patients	Virgili 2014	J Eur Acad Dermatol Venereol	Cohort study	147 females	MMF ointment 5 d a w for 4 w, then on alternate d for 4 we and the twice weekly for 4 w	12 w	Response: 113 patients (80.7%) non-responder: 27 women (19.3%)	
Vulvar lichen sclerosus: effect of maintenance treatment with a moisturizer on the course of the disease	Simonart 2008	Menopause	Prospective	34 females with VLS	0.1% betamethasone cream twice daily for 1 month then cold cream	At 1 m and then twice per y up to 11 y; median 58 m	Symptom-free after topical steroid treatment: 24/34 (of whom 18 had no worsening of symptoms on emollient alone) Partial response after topical steroid treatment: 10/34 (of whom 6 had no worsening of symptoms on emollient alone)	

New: Quality of Life in Vulvar Lichen Sclerosus Patients Treated with Long-Term Topical Corticosteroids	Wijaya 2021	J Low Genit Tract Dis	Retrospective survey data	136 females with biopsy proven VLS	Long-term (2 years or longer) TCS most class II in 98/136 females	Data collection after at least 2 y of therapy	Improvement in VLQI total score: Mdn 2.0 IQR 0.0-6.0 VLQI total score of 0-5 (minimal to no QoL impact): 0-5: 98/136 fully compliant with treatment 105/136 good disease control 120/136 stable disease 122/136 absence of scarring progression 127/136 Adverse events: 11/136 (erythema 10/136; dryness and irritability 1/136)	Study investigated differences in VLS patients who had not yet started TCS and patients who had been on long-term treatment with TCS (2 years or longer); data were extracted only from long-term arm 63 patients also had estrogen replacement therapy
Management of lichen sclerosus with triamcinolone ointment: effectiveness in reduction of patient symptom scores	LeFevre 2011	J Low Genit Tract Dis	Retrospective	34 females with biopsy proven VLS	Topical triamcinolone ointment	6 m	Complete symptom relief: 8/17 women with dyspareunia 19/22 women with vulval burning 23/32 women with vulval pruritus 12/13 women with vulval pain	Little information about signs
A therapeutic approach for female, relapsing genital lichen sclerosus: a single-centre study	Patsatsi 2013	J Dermatolog Treat	Retrospective	46 females	Methylprednisolone aceponate 0.1% once daily for 8 w	8 w	VAS and IGA median score was significantly decreased from baseline to week 8	Patients responsive to treatment (n = 38) were further treated with MPA 0.1% twice weekly (n = 15), tacrolimus once daily (n = 13) or topical emollient once daily (n = 10), as maintenance therapy until week 20
Long-term Management of Adult Vulvar Lichen Sclerosus: A Prospective Cohort Study of 507 Women	Lee 2015	JAMA Dermatol	Prospective longitudinal cohort study	507 females with biopsy proven VLS	TCSs of various potencies	M 4,7 y	150 patients (29.6%) were partially compliant 357 patients (70.4%)were compliant squamous cell carcinoma or vulval intraepithelial neoplasia occurred in 0 of the compliant patients vs. 7 (4.7%) of the partially compliant patients Suppression of symptoms occurred in 333 (93.3%) compliant patients vs. 87 (58.0%) partially compliant patients Adhesions and scarring occurred 12 (3.4%) compliant patients and 60 (40.0%) partially compliant patients Reversible TCS-induced cutaneous atrophy occurred in 4 (1.1%) compliant patients and 3 (2.0%) partially compliant patients	
Response of vulvar lichen sclerosus and squamous cell hyperplasia to graduated topical steroids	Clark 1999	J Reprod Med	Retrospective	84 females with VLS	Graduated topical steroids	6 m	62 percent were symptom free after 3 m	Subgroup analysis

New: Women's compliance with topical corticosteroids for the treatment of vulvar lichen sclerosus	Aguiar 2019	J. Low. Genit. Tract Dis.	Retrospective cohort study	332 women	TCS	10 y	Clinical improvement: 188/332 (58.2%)	Conference abstract
Lichen sclerosus of the vulva. Long-term steroid maintenance therapy	Sinha 1999	J Reprod Med	Prospective observational study	54 females with biopsy proven VLS	Graduated topical steroids for long-term maintenance	no information	51 responded to the steroid regimen, and three did not	Only abstract
Corticosteroid injections								
Lichen Sclerosus: Subdermal Steroid Injection Therapy. A Large, Long-Term Follow-Up Study	Baggish 2006	J Gynecol Surg	Retrospective	88 female with symptomatic VLS with poor response to initial treatment	Subdermal injections of 2 mg dexamethasone and 0.25% bupivacaine weekly then reduced slowly to every 2 months	Up to 54 m	72/88 pruritus free after 4 injections but 31 of those 72 patients (35.2%) required intermittent topical triamcinolone for pruritus relief	
Topical calcineurin inhibitors								
The effect of topical pimecrolimus on inflammatory infiltrate in vulvar lichen sclerosus	Kauppila 2010	Am J Obstet Gynecol	Cohort study	25 females with VLS	Topical 1% pimecrolimus cream twice daily for 8 w	8 w	19 of 25 had complete response and 1 a partial response. 5 had no response	
Pimecrolimus cream 1% in the treatment of lichen sclerosus	Nissi 2007	Gynecol Obstet Invest	Prospective	29 females with biopsy proven VLS, never achieved remission in adult life	Topical 1% pimecrolimus cream twice daily for up to 6 m	6 m	Of 26 who completed study, 42% in complete remission at 6 months. 50% experienced some side effects	
Pimecrolimus 1% cream in the treatment of vulvar lichen sclerosus in postmenopausal women	Oskay 2007	Int J Dermatol.	Prospective	16 post-menopausal symptomatic female with VLS	Topical 1% pimecrolimus cream twice daily for 3 m then as needed	12 m	Scoring of severity fell from 130 to 43 at 12 months. 11 had complete remission at 3 months but 4 had relapse	
Topical tacrolimus in the management of lichen sclerosus	Luesley 2006	BJOG	Prospective	16 symptomatic female with VLS partially responsive to steroids	Topical 0.1% tacrolimus twice daily for 3 m	12 m	2 complete response, 8 partial response and 6 no response and changed to other treatments	
Topical tacrolimus for recalcitrant vulvar lichen sclerosus	Sotiriou 2009	Eur J Dermatol	Cohort study	10 females with recalcitrant VLS	Topical 0.1% tacrolimus twice daily for 8 w	16 w	Symptoms improved from baseline level of 2.55 to 0.95 at 8 weeks, rose to 1.5 at last follow up visit. DLQI fell by 53%. Little effect on signs.	
Vulvar lichen sclerosus: 11 women treated with tacrolimus 0.1% ointment	Virgili 2007	Acta Derm Venereol	Prospective	11 female with VLS poor or non-response to topical steroids	Topical 0.1% tacrolimus ointment twice daily for 6 w then tapered	7 m	Complete response in 4 patients, good improvement in 4 and slight in 2. One failed to attend for follow up	

Topical retinoids								
Topical tretinoin in the treatment of vulvar lichen sclerosus: an advisable option?	Borghi 2015	Int J STD AIDS	Retrospective	17 female	Topical 0.025% tretinoin cream alternate days	24 w	35.3% and 17.6% achieved 75% improvement in subjective and objective scores respectively	
Open study of topical 0.025% tretinoin in the treatment of vulvar lichen sclerosus. One year of therapy	Virgili 1995	J Reprod Med	Prospective	22 female with biopsy proven VLS	Topical 0.025% tretinoin cream twice daily for 12 m	At least 12 m	75-78% improvement in symptoms. Hyperkeratosis improved 79%.	
New: Combined therapy in vulvar lichen sclerosus: does topical tretinoin improve the efficacy of mometasone furoate?	Borghi 2017	J. Dermatolog. Treat.	Retrospective, nonrandomized, comparative cohort study	21 women; 3 drop out	MMF ointment plus tretinoin 0.05% cream 5 consecutive d/w for 12 w	12 w	Responders: 13/21* GSS75: 8/21* (2 patients were asymptomatic) GOS75: 11/21* GGS50: 12/21* (2 patients were asymptomatic) GOS50: 16/21* very satisfied 9/21* moderately satisfied 5/21* Adverse events reported: 6/18 among others	
				20 women; 1 drop out	MMF ointment plus a cold cream 5 consecutive d/w for 12 w		Responders: 15/20* GSS75: 15/20* (4 patients were asymptomatic) GOS75: 12/20* GGS50: 15/20* (4 patients were asymptomatic) GOS50: 19/20* very satisfied 13/20* moderately satisfied 4/20* Adverse events reported: 2/19 among others	
Topical hormone preparations								
New: Assessing patient satisfaction and compliance with compounded clobetasol propionate 0.05% and estradiol 0.01% for the management of lichen sclerosus with coexisting genitourinary syndrome of menopause	Racher 2017	J Low Genit Tract Dis	Cohort study	17 females with VLS and coexisting genitourinary syndrome of menopause; (14 of the 17 subjects completed a short survey)	Clobetasol propionate and estradiol 0.01% in an emollient base	no information	Very satisfied: 85.7% more satisfied than with previous treatment: 92.9%	Conference abstract with little information; no information on previous treatment or treatment duration
Topical testosterone versus clobetasol for vulvar lichen sclerosus	Ayhan 2007	Int J Gynaecol Obstet	Retrospective	80 females with biopsy proven VLS	Topical testosterone propionate 2% in petrolatum first 6 w twice daily, following 6 w once daily. After optimal control of symptoms was achieved, a twice-weekly maintenance application was pursued for 3 months, and hence asneeded.	6 m	Remission: 77.5% Recurrence: 20%	
				60 females with biopsy proven VLS	Topical clobetasol proprionate cream first 6 w twice daily, following 6 w once daily.		Remission: 91.7% Recurrence: 6.7%	

					After optimal control of symptoms was achieved, a twice-weekly maintenance application was pursued for 3 months, and hence asneeded.			
Topical progesterone in the treatment of vulvar lichen sclerosus	Maina 2002	Ital J Gynaecol Obstet	Prospective	40 females with biopsy proven VLS	Topical 2.5% progesterone 25 mg twice daily for 2 w then once daily for 8 w	At least 3 m	At 3 months, 54.5% had complete resolution of symptoms, 33.3% had decrease in baseline scores with no change in 12%	
Effects of topical progesterone in vulvar lichen sclerosus	Michelletti 2001	Gynaecol Obstet	Prospective	20 females with biopsy proven VLS	Topical micronized natural progesterone cream 50mg twice daily for 4 w and then once daily for 8 w	12 w	14 women evaluable at 12 weeks. Resolution of symptoms in 57%. 50% showed an improvement in appearance. No histological change in the 8 patients who had repeat biopsy.	
PRP								
New surgical approach to lichen sclerosus of the vulva: the role of adipose-derived mesenchymal cells and platelet-rich plasma in tissue regeneration	Casabona 2010	Plast Reconstr Surg	Cohort study	15 females with biopsy proven VLS non-responsive to topical steroids	Treatment repeated once or twice after 3 m if needed	6-24 m	Itch and burning disappeared within 4 weeks. At 4 months, total clearance of symptoms and anatomy reported as normal.	
Use of Platelet-rich Plasma for Vulvovaginal Autoimmune Conditions Like Lichen Sclerosus	Behnia - Willison 2016	Plast Reconstr Surg Glob Open	Cohort study	28 females; 26 biopsy proven	3 platelet rich plasma treatments 4-6 w apart and again at 12 m	2-3 m after final treatment	Clearance of lesions in 28.6%, improvement in 60.7%; Clearance of symptoms 53.6%	
Laser								
New: Fractionated CO2 Laser as Therapy in Recalcitrant Lichen Sclerosus	Balchander 2020	J. Low. Genit. Tract Dis.	Retrospective case series	40 women who were symptomatic despite medical treatment	CO2 Laser at least 2 treatments	8 w	Eleven-Point Numerical Rating Scale MD: vaginal pain: -0.97 itching: -1.2 burning: -0.7 dryness: -1.77 dyspareunia, of those sexually active 30/40: -3.55 dysuria: -0.52 total symptom score MD: -7.81 disease activity after treatment white epithelium 6/40 perianal disease 5/40 erosions 1/40 fissures 2/40 among others	38 patients used additional an TCS 35 patients used additional vaginal estrogen
New: Fractional co2 laser treatment as adjunctive therapy to high-potency topical steroids for managing vulvar lichen sclerosus: Preliminary findings of a pilot study	Bartlett 2019	Menopause	Case series	11 women	CO2 Laser 3-5 treatments	1 y	Patients with 1-point improvement on 4-point scale after last treatment with regard to: sclerosis: 8/9 whitening: 9/11 parchment-like skin: 8/11	Subjects maintained their existing topical steroid and exogenous hormone treatment (no more

							elasticity: 7/10 lichenification: 5/8 moderate to severe labial fusion: 4/11 patients with 1-point improvement on 5-point scale after last treatment with regard to: quality of life : 10/11 sexual function: 7/8 dyspareunia: 6/8 among others	information); Conference abstract with little description of the outcomes
New: Carbon dioxide laser as a new valid treatment of lichen sclerosus	Teodoro 2019	Clin. Exp. Obstet. Gynecol	Case series	10 females with hyperkeratotic VLS	CO2 laser 1-3 treatments	3 m	VAS 0-10 pruritus bl: 8.5±2.22; 3 m: 1.2±1.47 dyspareunia bl: 6±3.13; 3 m: 2.3±2.41 burning bl: 5.7±2.21; 3 m: 0.8±1.32 urinary problems bl: 1.6±2.32; 3 m: 0.3±0.95	
New: The short-term efficacy and safety of fractional CO2 laser therapy for vulvovaginal symptoms in menopause, breast cancer, and lichen sclerosus	Gardner 2021	Menopause	Retrospective chart review	31 females with VLS	CO2 laser 3 treatments	Mean follow-up of 13.8 w (all patients, not subgroup)	Mean FSFI: bl 11.6, post treatment 15.1	Subgroup analysis
New: Effect of rescue fractional microablative CO2 laser on symptoms and sexual dysfunction in women affected by vulvar lichen sclerosus resistant to long-term use of topic corticosteroid: a prospective longitudinal study	Pagano 2020	Menopause	Prospective cohort study	40 females older than 35 with biopsy proven VLS	CO2 laser 2 tretaments	Median follow-up: 5m	Mdn (IQR) VAS vulval itching: bl 8 (7-9); after treatment: 3 (1-4) VAS vulval dryness: bl 8 (8-9); after treatment: 3 (1-5) superficial dyspareunia: bl 9 (7-10); after treatment: 3 (2-6) reduced sensitivity during intercourse: bl 6 (3-9); after treatment: 2 (0-3.25) vulvodynia: bl 0 (0-7); after treatment: 1 (0-3)	Only included women who were resistant to long-term use of TCS
Fractional CO2 Laser Treatment for Vaginal Atrophy and Vulvar Lichen Sclerosus	Baggish 2016	J Gynecol Surg	Prospective	27 females with biopsy proven VLS with symptoms	CO2 laser 3 treatments	No information	24/27 reported resolution of symptoms and 26 demonstrated improvement in clinical signs	
New: Use of Er:YAG laser in the treatment of vulvar lichen sclerosus	Gómez-Frieiro 2019	Int. J. Women's Dermatol	Cohort study	28 women with symptomatic VLS	Er:YAG laser 3 treatments	No information	Impact on life before treatment (0-10): 5.36±2.25 impact on life after treatment (0-10): 1.57±1.4 total score clinical signs before treatment (0-14): 9.32±2.51 total score clinical signs after treatment (0-14): 4.36±2.34 among others	
Photodynamic therapy								
New: 5-Aminolevulinic acid photodynamic therapy in refractory vulvar lichen sclerosus et atrophicus: series of ten cases	Lan 2018	Photodyn. Ther.	Case series	10 postmenopausal or perimenopaus	ALA-PDT	6 m	VAS 0-3 M -itching: bl: 2.6; 6 m: 0.1 -pain: bl: 2.0; 6 m: 0 -dyspareunis: bl: 1.0; 6 m: 0 DLQI: bl: 19; 6 m: 2	No information on SD available

				al female with VLS			Serious adverse events: 0/10 among others	
New: Evaluation of the efficacy of 5-aminolevulinic acid photodynamic therapy for the treatment of vulvar lichen sclerosus	Li 2019	Photodyn. Ther.	Retrospective cohort study	10 females with VLS	ALA-PDT	6 m	TSS: 11.4 --> 4.9 Pruritus: 4.8 -->2 TOS: 4.3 --> 2 DLQI: 13.4 --> 5.9 FSFI: 8.5 --> 17.67	Result table not available as mentioned in the text
New: Clinical and Dermoscopic Assessment of Vulvar Lichen Sclerosus After 5-Aminolevulinic Acid Photodynamic Therapy:A Prospective Study	Liu 2021	Photodyn. Ther.	Prospective cohort study	24 females with VLS	ALA-PDT	6 treatments	Median (1Q 3Q) lesion size (0-10) baseline: 5.00 (3.00; 8.00); post-3rd: 4.00 (2.25; 7.00); post -6th: 3.00 (1.00; 5.75) depigmentation (0-3) baseline: 2.00 (2.00; 3.00); post-3rd: 2.00(1.00; 2.00); post -6th: 1.00 (1.00; 2.00) Itching VAS: baseline: 8.00 (7.00; 9.00); post-3rd: 4.00 (2.25; 6.00); post -6th: 1.00 (0; 4.00) burning pain VAS: baseline: 1.00 (0; 4.75); post-3rd: 0 (0; 1.75); post -6th: 0 (0; 0)	
New: Photodynamic Therapy in the Treatment of Vulvar Lichen Sclerosus	Maździarz 2017	Photodyn. Ther.	Prospective cohort study	102 females with biopsy proven VLS	ALA-PDT	12 m	Very satisfied: 62/102 satisfied: 17/102 some improvement: 10/102 not satisfied: 13/102 worsening: 0/102 regression in lichenification with hyperkeratosis: 48/93 regression in atrophic lesions: 34/91 regression in subepithelial ecchymoses and teleangiectases: 15/19 regression in erosions and fissures: 44/62	Included patients failed to respond to treatment with clobetasol or did not agree to topical steroids
New: ALA- photodynamic treatment in Lichen sclerosus—Clinical and immunological outcome focusing on the assessment of anti-nuclear antibodies	Olejek 2017	Photodyn. Ther.	Prospective cohort study	60 females with LS without concomitant autoimmune disease = group I 40 females with LS with concomitant autoimmune disease = group I)	ALA-PDT	2 y	Symptoms intensity (0-no, 1-moderate, 2-severe) group I: bl 1.77±0.87; after PDT: 0.60±0.16 group II: bl: 1.73±0.86; afer PDT: 0.60±0.13	
New: 5-ALA-photodynamic therapy in refractory vulvar lichen sclerosus et atrophicus	Zhang 2020	Int J Clin Exp Pathol	Cohort study	30 femals with VLS and routine	ALA-PDT	6 m	VAS itching bl: 2.4±0.82; 6 m: 0.17±0.59 VAS pain: bl: 0.1±0.40; 6 m: 0±0.00 VAS dyspareunia bl: 1.23±0.77; 6 m: 0.07±0.37 clinical manifestation score: bl: 9.73±2.47; 6 m: 1.23±1.65	

				treatment failure			no severe adverse events Adverse events: pain 30/30; burning sensation 29/30; erythema 28/30; swelling 29/30 among others	
New: Does HPV infection have impact on results of photodynamic treatment of vulvar lichen sclerosus?	Zielińska 2020	Photodyn. Ther.	Prospective cohort study	73 females with VLS (17 HPV+; 56 HPV-)	ALA-PDT	2 y	Remission = Pain VAS 0-3 73/73 Mean of remission period HPV +: 11 ± 9 m Mean of remission period HPV +: 14± 9 m	
Therapeutic effects of 5-ALA-induced photodynamic therapy in vulvar lichen sclerosus	Biniszkiewicz 2005	Photodiagnosis Photodyn Ther	Cohort study	24 female with symptomatic VLS	ALA-PDT	No information	17 patients had complete resolution of itching	No information on effect on signs
Photodynamic therapy of vulvar lichen sclerosus with 5-aminolevulinic acid	Hillemanns 1999	Obstet Gynecol	Prospective	12 female with biopsy proven VLS with pronounced pruritus	ALA-PDT	6 m	At 6-8 weeks' F/up, mean values for pruritus reduced from 2.6 to 1.0. Duration of symptom reduction was 3-9 months. At 6-month F/up 7 of 10 had symptomatic relief. no improvement in clinical appearances	
Sexual functions and depressive symptoms after photodynamic therapy for vulvar lichen sclerosus in postmenopausal women from the Upper Silesian Region of Poland	Skrzypulec 2009	J Sex Med	Cohort study	27 female with biopsy proven VLS	ALA-PDT	3 m	FSFI reduced from 24.6 to 15.9 and beck depressive index fell from 12 to 9. Lubrication disorders increased. No significant difference in depressive symptoms	No detail about clinical improvement
New: Photodynamic therapy with green light for the treatment of vulvar lichen sclerosus – preliminary results	Osiecka 2017	Photodyn. Ther.	Cohort study	11 females with VLS	ALA-PDT with green light	6 m	Itching bl: moderate: 4/11, severe 7/11; 2 m: lack: 9/11, weak 1/11, moderate 1/11; 4 m: lack 8/11, weak 2/11, moderate 1/11; 6 m: lack 7/11, weak 3/11, moderate 1/11 Burning bl: 5/11; 2 m: 0/11; 4 m: 1/11; 6 m: 2/11 erosions bl: 5/11; 2 m: 0/11; 4 m: 1/11; 6 m: 2/11 pain bl: 3/11; 2 m: 1/11; 4 m: 1/11; 6 m: 2/11	Patients were refractory to various topical therapies
Surgery								
New: Outcome of perineoplasty and de-adhesion in patients with vulvar Lichen sclerosus and sexual disorders	Lauber 2021	Eur. J. Obstet. Gynecol.	Retrospective observational study	41 females with VLS with undergone perineoplasty	Perineoplasty according to modified Fenton's procedure	1-5 y	Sexually active postoperatively 26/41 pain during intercourse postoperatively: 10/41 dyspareunia: 10/27 improvement in sexual life: 28/41 very satisfied 22/41 satisfied 15/41 not satisfied 3/41 no information 1/41 ability to orgasm postoperatively: 33/41 recommendation of surgery: 29/41	Retrospective analysis of questionnaire data, 18 patients were treated with additional de-adhesion
New: Surgical treatment of disabling conditions caused by anogenital lichen sclerosus in women: An account of	Rangatchew 2017	J. Plast. Reconstr.	Retrospective case series	38 females with LS	Surgery In 88% of cases local exzision	No information	Dyspareunia: very large benefit: 5/24; large benefit: 6/24; benefit: 5/24; slight benefit: 2/24; no benefit: 6/24 anogenital symptomatic complaints: very large benefit: 4/23; large benefit:	Several of the 38 patients included in the study underwent

surgical procedures and results, including patient satisfaction, benefits, and improvements in health-related quality of life		Aesthet. Surg.		surgically treated	in 9% and 3% of cases partial and total vulvectomies, respectively		6/23; benefit: 7/23; slight benefit: 2/23; no benefit: 4/23 disease-related confidence/self-esteem: better 9/27; no change 17/27; worse 1/27 disease-related mental well-being: better 9/27; no change 16/27; worse 2/27 sex life: better 15/26; no change 8/26; worse 3/26 body image: better 8/27; no change 17/27; worse 2/27 among others	more than one surgery
A Qualitative Study on Experiences After Vulvar Surgery in Women With Lichen Sclerosus and Sexual Pain	Brauer 2016	J Sex Med	Retrospective	19 females with biopsy proven VLS	posterior vestibuloplasty n=19 In addition, four patients underwent an anterior vestibuloplasty and four patients underwent correction of clitoral phimosis	No information	13/19 (68%) reported improvement in dyspareunia 18/19 (95%) reported improvement in symptoms in daily life	Post-surgery for scarring and dyspareunia secondary to LS
Vulvar lichen sclerosus: A new regenerative approach through fat grafting	Boero 2015	Gynecol Oncol	Cohort study	36 females with VLS Failure to respond to first line treatment	Fat grafting – 1-3 procedures	12 m	34/36 (94%) improved appearance and symptoms. 34/36 (94%) able to stop using topical steroids	
Perineoplasty for the treatment of introital stenosis related to vulvar lichen sclerosus	Rouzier 2002	Am J Obstet Gynecol	Retrospective	64 females with biopsy proven VLS with introital stenosis	Perineoplasty	Median: 34 m	46/50 (92%) relief of dyspareunia 43/50 (86%) improvement in quality of intercourse	12 were lost to follow-up and 2 patients did not respond to the questionnaire
New surgical approach to lichen sclerosus of the vulva: the role of and platelet-rich plasma in tissue regeneration	Casabona 2010	Plast Reconstr Surg	Cohort study	15 females with biopsy proven VLS non-responsive to topical steroids	Treatment repeated once or twice after 3 m if needed Grafting of adipose-derived stem cells and injection of platelet rich plasma; treatment repeated once or twice after 3 m if needed	6-24 m	Itch and burning disappeared within 4 weeks. At 4 months, total clearance of symptoms and anatomy reported as normal.	
Others								
New: Prospective observational study of the efficacy of mixed methylene blue compound injection for treatment of vulvar non-neoplastic epithelial disorders	Li 2019	Int J Gynaecol Obstet	Prospective observational study	64 females with VLS	Intradermal methylene blue injections	2 y	VAS itching baseline: 7.85±1.61; 1 m: 1.85±2.56; 3 m: 1.62±2.59; 6 m: 2.20±3.09; 12 m: 2.33±3.08; 24 m: 2.60±3.26 SHAP baseline: 29.50±19.80; 1 m: 28.20±19.31; 3 m: 23.25±19.44; 6 m: 20.93±20.08; 12 m: 20.13±20.49; 24 m: 20.10±20.50	Subgroup analysis; Methylene blue compound injection comprise methylene blue injection, dexamethasone powder-injection, ropivacaine injection and normal saline injection
Avocado and soybean extracts as active principles in the treatment of mild-to-moderate vulvar lichen sclerosus: results of efficacy and tolerability	Borghi 2015	J Eur Acad Dermatol Venereol	Prospective	23 females with mild - moderate VLS	Avocado and soya bean extract cream twice daily and dietary supplement for first 12 weeks	24 w treatment duration	12 and 13 patients achieved at least 75% improvement in subjective and objective global scores, respectively	
All ages								

TCS								
New: Lichen Sclerosus in Prepubertal Girls: An Uncommon but Treatable Cause of Lower Urinary Tract Symptoms	Arlen 2020	Urology	Case series	10 girls with LS associated LUTS	Clobetasol propionate twice daily for 2 w, then daily for 2 w, then Triamcinolone ointment twice daily for 2 w, then daily for 2 w	8 w	LUTS improvement 8/10 unchanged voiding symptoms 2/10	
Treatment of vulvar lichen sclerosus with topical corticosteroids in children: a study of 72 children	Casey 2015	Clin Exp Dermatol	Cohort study	72 girls with VLS (age 3-14)	Clobetasol proprionate daily for 3 m		Clobetasol propionate 0.05% (n=72) compared with a retrospective study of 31 girls treated with moderately potent topical steroids. Clobetasol propionate superior (72.6% versus 32.2% clearance of symptoms)	
New: Features of the course and therapy of lichen sclerosus of the vulva with identified human papillomavirus infection	Chernova	Klinicheskaya Dermatologiya i Venerologiya	Cohort study	29 females with LS and papillomavirus infection without clinical manifestation	High potency TCS	4 m	Elimination of itching after 1 m: 18/29 absence of its progression after 4 m: 22/29	All patients had LS and an HPV infection data only from the abstract; (paper is in Russian); patient age was not mentioned
				30 females with LS and papillomavirus infection without clinical manifestation	High potency TCS and antiviral treatment (purified extract of Solanum tuberosum plant shoots locally and systemically)		Elimination of itching after 1 m: 25/30 absence of its progression after 4: 26/30	
				27 females with LS and papillomavirus infection without clinical manifestation	Antiviral treatment and lasertophoresis (purified extract of Solanum tuberosum plant shoots locally and systemically)		Elimination of itching after 1 m: 25/27 absence of its progression after 4: 26/27	
New: Risk of cutaneous fungal infections associated with long term use of topical corticosteroids in vulvar lichen sclerosus	Melo 2019	J Low Genit Tract Dis	Retrospective cohort study	332 females with VLS	Diffrent TCS	10 y	cutaneous fungal infections: 77/332	Conference abstract with little information; mean age at diagnosis: 55 y
Does treatment of vulvar lichen sclerosus influence its prognosis?	Cooper 2004	Arch Dermatol	Cohort study	253 adult females, 74 girls	Diffrent TCS		In 244 patients (96%) symptoms improved with treatment 168 (66%) became symptom free 76 (30%) showed partial response 11 (4%) had poor response	
Laser								
New: The clinical analysis of fractional co2 laser in the treatment of vulvar lichen sclerosus	Li 2018	J Low Genit Tract Dis	Prospective cohort study	42 females with VLS	CO2 laser 3 -5 treatments	3-12m	Improvement in symptoms: 38/42 overall satisfaction rate: 40/42 VAS pruritus: bl: 6.75±1.79; after teratment: 1.78±1.36 VAS dyspareunia: bl: 4.88±2.79; after teratment: 2.15±1.29 no adverse events due to treatment amng others	Conference abstract with little information patient age was not mentioned

Surgery								
New: Evaluating in office surgery followed by platelet rich plasma to treat lichen sclerosus	Posey 2019	J Low Genit Tract Dis	Cohort study	38 females with adhesions due to VLS	Adhesiolysis followed by PRP	no information	Full remission: 16% marked improvement: 74% no improvement: 10%	Conference abstract patient age was not mentioned
A new, hydrodissection with reverse V-plasty technique for the buried clitoris associated with Lichen Sclerosus	Ostrzenski 2010	Gynecol Surg	Sequential study	8 adult female and 2 girls (age 15-16)	Hydrodissection and reverse V-plasty for clitoral burial	5 y	No recurrence of adhesions at 5 years. Improvement in clitoral pain	
New: Safety and Efficacy of Stromal Vascular Fraction Enriched Fat Grafting Therapy for Vulvar Lichen Sclerosus	Monreal 2020	Cureus	Retrospective cohort study	39 female age 13-69 with VLS	Autologous fat grafting enriched with adipose derived stromal vascular fraction cells	2 y	mVVSQ symptoms (0-40): bl: 21.18± 9.51; 6 m: 11.92± 6.83; 24 m: 8.46± 7.28 signs (0-40): bl: 16.90±8.71; 6 m: 8.97± 6.01; 24 m: 7.51±5.96 social Function (0-80): bl: 39.85±20.90; 6 m: 25.64±17.97; 24 m: 19.18±18.36 sexual function (0-30): bl: 15.64±10.58; 6 m: 10.05±8.24; 24 m: 8.44±7.95 global (0-190): bl: 93.56±33.97; 6 m: 56.56±28.70; 24 m: 43.59±28.23 no adverse events were reported	
PRP								
New: Intradermal injection of autologous platelet-rich plasma for the treatment of vulvar lichen sclerosus	Goldstein 2017	J. Am. Acad. Dermatol.	Cohort study	15 patients with biopsy-proven VLS 12 complete study	PRP 2 treatments	6 w	M±SD IGA (0-3): bl: 2.67±0.49; 6w 1.83±0.83 adverse event: 0/12	Letter to the editor patient age was not mentioned
Cryotherapie								
Cryosurgery--the last resort or a surgical alternative in the treatment of lichen sclerosus et atrophicus of the vulva (LSAV)?	Kastner 2003	J Dtsch Dermatol Ges.	Cohort study	22 adult female with VLS 9 girls with VLS (age 5-15)	Cryotherapy	No information	All patients experience improvement in signs and symptoms. 5 required second cycle after an average of 10.6 m and two patients a third treatment complete remission 1/17 clinical improvement 16/17	Follow up data only for 17/31 patients available
Others								
New: Short- and long-term efficacy of focusedultrasound therapy for non-neoplastic epithelialdisorders of the vulva	Wu 2017	BJOG	Retrospective observational study	44 females wit VLS not younger than 14 y	Focused ultrasound	5y	Therapeutic Index ≥ 90% = cured: 23/44 therapeutic Index 21–89% = effective: 17/44 therapeutic Index ≤ 20% = ineffective: 4/44 recurrence rate: 12/44	Subgroup analysis

b. Men and boys with genital disease

Titel	**First author Year**	**Journal**	**Study design**	**Study population**	**Intervention**	**follow up**	**Outcome**	**Notes**

Age 0-12 years								
Age 13-17 years								
Age 18+								
TCS								
New: Conservative Management of Lichen Sclerosus Male Urethral Strictures: A Multi-Institutional Experience	Rozanski 2021	Urology	Retrospective chohort study	112 men with lichen sclerosus urethral stricture disease with conservtive treatment regimes	Conservative treatment regimes without operations (e.g. urethral balloon dilation)	Median 30 m (IQR 12-55,5)	Clean intermittent catheterization with intraurethral steroids failure: 5/16 clean intermittent catheterization without intraurethral steroids failure: 8/35	Subgroup analysis with little extractable data
Treatment of male genital lichen sclerosus with clobetasol propionate and maintenance with either methylprednisolone aceponate or tacrolimus: a retrospective study	Kyriakou 2013	J Dermatolog Treat	Prospective	41 males with biopsy proven genital LS	Clobetasol propionate twice daily for 8 w, then either tacrolimus 0.1% once daily or methylprednisolone 2 per w 0.1% for 12 w	end of clobetasol propionate treatment	Pruritus VAS mean (SD) Pre-treatment: 4.08 (0.92), median 5; 8 weeks: mean 1.24 (1.33), median 1 IGA mean (SD) Pre-treatment: 2.29 (0.46), median 2; 8 weeks: mean 0.56 (0.8), median 0 DLQI mean (SD) Pre-treatment: 16.53 (2.95), median 17 8 weeks: 5.29 (4.61), median 4	Data for clobetasol propionate only
Penile lichen sclerosus et atrophicus treated with clobetasol dipropionate 0.05% cream: a retrospective clinical and histopathological study	Dahlman-Ghozlan 1999	J Am Acad Dermatol	Retrospective	22 males with penile LS	Clobetasol propionate once daily/twice daily	M 14.6 m	Symptoms: 23% clear, 41% improved Signs: 43% clear Questionnaire 0-4 (0 = none to 4 = severe) Sexual function: Dyspareunia 2.67 to 1.61 Erectile pain 2.67 to 1.67 Improvement in urinary flow 2.25 to 1.83	Complication genital herpes Patient assessment for 7 symptoms or signs
Early aggressive treatment of lichen sclerosus may prevent disease progression	Tausch 2012	J Urol	Retrospective	43 males	Clobetasol propionate twice daily progression to circumcision, meatoplasty and urethroplasty	M 44 m	7/13 patients successfully treated with topical steroid Rest had surgical tretaments	
Intraurethral Steroids are a Safe and Effective Treatment for Stricture Disease in Patients with Biopsy Proven Lichen Sclerosus	Potts 2016	J Urol	Retrospective	28 males with urethral stricture due to LS (biopsy proven)	Intraurethral clobetasol propionate via catheter or meatal dilator twice daily	25 m	25/28 (89%) success rate with no further surgical intervention (Restoration urinary function)	Majority needed continuous occasional treatment, except 3.
Laser								
New: Fractional CO2 laser therapy of lichen sclerosus in males: a new therapeutic opportunity?	Ferrara 2020	J. Dermatol. Treat.	Prospective cohort study	10 males with penile LS	CO2 laser 3 treatments	6 m	DLQI: bl: 11.2 ±5.5; 6m: 4.3 ± 3.3 MSHQ: bl: 94.3±20.1; 6m: 107.3 ± 15.9 MenLas Patient: bl: 29.5±6.4; 6m: 15 ± 4.9 MenLas Observer: bl:13.6±4.5; 6m: 6 ± 2.7	

							significant adverse events: 0/10 among others	
Is carbon dioxide laser treatment of lichen sclerosus effective in the long run?	Windahl 2006	Scand J Urol Nephrol	Retrospective	62 males with penile LS 50/62 in lomg term follow up	CO2 laser 1 treatment	M 14 y	No local symptoms 40/50 Minor residual symptoms 8/50 Retreated (2004) 2/50	
Surgery								
New: Dorsal onlay urethroplasty using lingual mucosal grafts for lichen sclerosis anterior urethral strictures repair: Long-term outcomes	Aldaqadossi 2020	Int. J. Urol.	Case series	36 men with LS and long anterior urethral stricture	Dorsal onlay urethroplasty using lingual mucosal graft	5 y	Qmax mL/s Mdn (IQR) before surgery: 5 (4-7) after 1y: 18 (18–20) after 2y: 18 (17–19) after 3y: 17 (16–18) after 4y: 17 (16–18) after 5y: 17 (16–17) postoperative complications: 4/34	All patients had from LS long anterior urethral strictures
New: The buccal belt: a buccal mucosal graft sub-coronal resurfacing for recurrent penile adhesions in patients with lichen sclerosus	Beamer 2020	Int Urol Nephrol	Retrospective case series	21 men with LS and refractory penile adhesions	Sub-coronal buccal mucosal graft (BMG) resurfacing	1 y	Overall improvement of symptoms on GRA (-3 = markedly worse to +3 = markedly improved): +3: 12/21; +2: 6/21; +1: 3/21 esthetic appearance GRA: +3: 9/21; +2: 9/21; +1: 1/21; 0: 1/21; -1/1/21 improved in bleeding GRA: +3: 8/21; +2: 3/21; +1: 7/21; 0: 3/21 bleeding w/intercourse GRA: +3: 8/21; +2: 9/21; +1: 1/21; 0: 3/21 change in SHIM worsened (≥3 points) 1/20 unchanged (within 3 points) 9/20 improved (≥3 points) 10/20 Visual Analog Scale—functional outcome: 9.0 (6-10) Visual Analog Scale—esthetic outcome: 8.9 (7-10) among others	
New: Repair of panurethral stricture: Proximal ventral and distal dorsal onlay technique of buccal mucosal graft urethroplasty	Chodisetti 2018	Arab J. Urol.	Cohort study	31 men with LS and panurethral stricture	Buccal mucosal graft (BMG) urethroplasty	1 y	Sucsess rate: 25/31	Subgroup analysis
New: The Technique of double faced dorsal onlay and ventral inlay graft penile urethroplasty in complex pan-urethral strictures	Pardeshi 2020	Indian J Urol	Cohort study	37 men severe meatal stenosis and very narrow	Combined Ventral inlay and dorsal onlay BMG penile urethroplasty	No information	No issues: 32/37 with average maximum flow of 18ml/sec development of recurrent meatal stenosis: 3/37 mild degree of erectile dysfunction: 8/37	Conference abstract with little information on outcomes; patients

				penile urethra due to inactive LS				with active LS were excluded
The surgical management of lichen sclerosus of the glans penis: our experience and review of the literature	Garaffa 2011	J Sex Med	Retrospective	31 males with genital LS of glans penis	Glans resurfacing – total or partial SSG from thigh	M 12.8 m	84% improvement – Pt GA 71% improvement in sexual function Pruritus/pain 90% improvement – QOL	
Heroic measures may not always be justified in extensive urethral stricture due to lichen sclerosus (balanitis xerotica obliterans)	Peterson 2004	Urology	Retrospective	63 males with urethral stricture due to LS	Stricture repair /Perineal urethrostomy	M 38 m	52/63 patients opted for perineal urethrostomy and were happy with outcome Adverse effect 4/36	
Outcome of 1-stage urethroplasty using oral mucosal grafts for the treatment of urethral strictures associated with genital lichen sclerosus	Xu 2014	Urology	Retrospective	36 males with urethral stricture due to LS	Stricture repair using either BMM or lingual MM	M 39 m	90% success –urinary flow rate.	
Urethral reconstruction of long-segment lichen sclerosus strictures: Comparison of surgical techniques and outcomes	Rourke 2012	J Urol	Retrospective	39 males with urethral stricture due to LS	Urethral stricture Surgery 1. Staged reconstruction (14) 2. One-stage on-lay reconstruction (13) 3. Urethrostomy (12)	40 m	1. 79% success 2. 54% success 3. 92% success (p=0.04 when compared to One-stage on-lay) ii) Persistence of urinary symptoms (6 months) 1. 21%; 2. 62%; 3. 8% urethral patency on cystoscopy 1. 92%; 2. 83%; 3. 100%	Conference abstract Shows success with urethrostomy
Treatment of urethral strictures in balanitis xerotica obliterans (BXO) using circular buccal mucosal meatoplasy: experience of 15 cases	Simsek 2014	Arch Ital Urol Androl	Retrospective	12 males with urethral (distal) stricture due to LS	Meatoplasty with buccal MM graft	M 21 m	Consistent improvement in urinary peak flow rate pre-treatment peak flow rate = 4.18 ml/s mean; post-treatment = 22.4 ml/s mean at 1 month no stricture recurrence at Follow up	
Urethral reconstruction in balanitis xerotica obliterans	Trivedi 2008	Urol Int	Retrospective	152 males with urethral stricture due to LS	Graft repair of urethral stricture using skin or oral mucous membrane, ventral onlay	12 m	All grafts overall success rate = 57%. Mucosal grafts 92% success rate. Measured by uroflowmetry at 3 months and 1 year	
Primary dorsal buccal mucosa graft urethroplasty for anterior urethral strictures in patients with lichen sclerosus	Acimovic 2016	Int Urol Nephrol	Retrospective	32 males with urethral stricture due to LS	BMG graft repair of urethral stricture using dorsal urethroplasty (23) or 2-stage repair (9)	M 28 m	Assessed uroflowmetry mean (range). Pre-treatment 6.2 ml/min (2.6-10.2); post-treatment (9 months) 18.2 ml/min (15.8 – 21.2) assessed need for further intervention - 90.6% had good result complications – 9.4%, haematoma and fistula	No difference in results between I and 2 stage repair

Lichen sclerosus et atrophicus of the penis Review of 10 cases treated by complete circumcision	Monteiro 2002	Skin Cancer	Retrospective	10 males with LS treated with circumcision	Surgery	11 m - 3 y	9 clear, 1 improved PGA	Retrospective review of case notes
Others								
Genital Lichen Sclerosus in Male Patients: A New Treatment with Polydeoxyribonucleotide	Zucchi 2016	Urol Int	Prospective	24 males with penile LS	Polydeoxyribonucleotide 5 - 10mg intradermally weekly	M 16 m	No change in sexual function (IIEF-5 scoring) mean (SD) pre-treatment 19.62 (6.99) post-treatment 20.24 (7.69) Pt GA 80% improved DLQI (QOL) improved mean (SD); Pre-treatment 17.14 (8.16); post-treatment 9.57 (9.21)	
all ages								
TCS								
Clinical parameters in male genital lichen sclerosus: a case series of 329 patients	Edmonds 2012	J Eur Acad Dermatol Venereol	retrospective	329 males (age 3-38) 185 were treated with clobetasol alone	Clobetasol propionate twice daily for 4 w, repeated up to 3 times	n/a	In 109/185 (59%) men medical treatment was adjudged a success. 90/185 (49%) responded to topical steroids at F/up	
Long-term efficiency of skin stretching and a topical corticoid cream application for unretractable foreskin and phimosis in prepubertal boys	Ghysel 2009	Urol Int	Prospective	462 boys; age: 0-17 Subgroup 27 patients with LS	Betamethasone 0.05% cream once daily or twice daily plus skin stretching to achieve retraction of foreskin	M 22 m	383/462 developed retractable foreskin LS cases 18/27 (67%) response – PGA	Phimosis study with LS subset analysis
The response of clinical balanitis xerotica obliterans to the application of topical steroid-based creams	Vincent 2005	J Pediatr Surg	Cohort study	56 boys; age: 4-15 with phimosis due to LS	Moderate potency topical steroids (2.5% hydrocortisone, Tri-adcortyl®)	3 m	Clear 18% -PGA improved 12% PGA minimal, no improvement or worse 70% - PGA	
Topical calcineurin inhibitors								
Safety and tolerability of adjuvant topical tacrolimus treatment in boys with lichen sclerosus: a prospective phase 2 study	Ebert 2008	Eur Urol	Prospective	20 boys ; age: 5-16 with phimosis due to LS, treated with circumcision	Tacrolimus 0.1% ointment twice daily for 3 w repeated if necessary, post circumcision to prevent relapse	M 17 m	9/20 had active LS post circumcision. (11 had disease only confined to the foreskin). Disease cleared at 3 weeks. One relapsed and cleared with further course of tacrolimus 20 patients clear at F/up – PGA and DLQI	Incidence of LS in circumcision series was 19.4%
PRP								
New: Autologous platelet-rich plasma (PRP) in chronic penile lichen sclerosus: the impact on tissue repair and patient quality of life	Casabona 2017	Int Urol Nephrol	Case series	45 males refractory to clobetasol or requested an	PRP	M 17.60 ± 5.63 m	MD: IGA (0 = cleared—no inflammatory signs to 5 = severe—severe erythema, infiltration, lichenification, and excoriation): 2.04 ± 0.71 MD: DLQI (0=no effect on patient's life to 30= extremely large effect): 7.73 ± 4.92	Diffrent numbers of treatments, range 2 to 10, Mdn: 4

				alternative treatment				
Surgery								
New: Utility of uroflowmetry during the follow-up of children affected by balanitis xerotica obliterans (BXO)	Arena 2018	Archivio Italiano di Urologia e Andrologia	Case series	75 circumcised patients; age 5-15	Circumcision and clobetasol propionate		Qmax mL/s M±SD 2 w: 10.1 ± 3.3 6 m: 11.9 ± 3.3 1 y: 13.0 ± 2.5 2 y: 14.8 ± 2.2	Retrospective subgroup analysis of 75 LS patients out of 180 circumcised patients
Foreskin preputioplasty and intralesional triamcinolone: a valid alternative to circumcision for balanitis xerotica obliterans	Wilkinson	Journal of Pediatric Surgery	Retrospective	136 boys underwent primary surgery for histologically confirmed BXO; median age at surgery was 9 years (IQR, 7-11)	Foreskin preputioplasty (n=104) Circumcision (n=32)	Median follow-up: 14 m; ICR 2.5-17.8	Normal macroscopic appearance (fully retractile foreskin if present and no macroscopic evidence of BXO): 84/104 (81%) Normal macroscopic appearance (fully retractile foreskin if present and no macroscopic evidence of BXO): 23/32 (72%)	

c. Mixed (females and males) with genital disease

Titel	First author Year	Journal	Study design	Study population	Intervention	follow up	Outcome	Notes
Age 0-12 years								
Age 13-17 years								
Age 18+								
PRP								
New: Platelet-rich plasma for genital lichen sclerosus: analysis and results of 94 patients. Are there gender-related differences in symptoms and therapeutic response to PRP?	Tedesco 2020	J Dermatolog Treat	Cohort study	51 females with VLS	PRP	6 m	Itching bl: 80.4%; 6 m: 21.6% pain: bl: 33.3%; 6 m: 7.8% burning sensation bl: 51%; 6 m:15.7% dyspareunia bl: 37.3%; 6 m: 31.4% DLQI: bl median: 6 min:0 max: 20; 6 m: median: 3 min: 0 max:9 among others	Early stage: 33.3% late stage: 67.7%

				43 males with genital LS			Itching bl: 37.2%; 6 m: 9.3% pain: bl: 18.6%; 6 m: 4.7% burning sensation bl: 23.3%; 6 m: 2.3% dyspareunia bl: 34.9%; 6 m: 11.6% DLQI: bl median: 6 min:0 max: 14; 6 m: median: 4 min: 0 max:8 among others	Early stage: 53.5% late stage: 46.5%
Laser								
Treatment of lichen sclerosus with carbon dioxide laser vaporization	Kartamaa 1997	Br J Dermatol	Retrospective	10 patients with LS	CO2 laser 1 treatment	8 m - 5 y	Asymptomatic 6/10 Improvement 3/10 Recurrence 1/10	3 women had extragenial LS
Other								
Treatment of genital lichen sclerosus with topical calcipotriol	Gupta 2005	Int J STD AIDS	Prospective	23 patients with genital LS	Topical 0.005% calcipotriol ointment once daily for 1 w and then twice daily if tolerated	16 w	Improvement in symptoms (4.8 to 1.8) and signs (3.4 to 2) at 16 weeks	
Treatment of lichen sclerosus with antibiotics	Shelley 2006	Int J Dermatol	Cohort study	15 adults with genital LS	Penicillin oral or im	n/a	Improvement (2 cleared, 3 result favourable)	4 cases were extragenital
all ages								
Topical calcineurin inhibitors								
Multicentre, phase II trial on the safety and efficacy of topical tacrolimus ointment for the treatment of lichen sclerosus	Hengge 2006	Br J Dermatol	Prospective	84 patients with biopsy proven LS	Tacrolimus 0.1% ointment twice daily	18 m	Results in male/female/EG not distinguished 77% showed partial or complete improvement PGA complete response 16% at 16 weeks, 43% at 24 weeks symptoms – significant improvement symptom score mean (SD) pretreatment 3.7(2.9); post-treatment at week 16 2.1 (2.2);	Attrition (n=14) at 16 weeks, (n=32 at 18 months) Rates of improvement similar in m/f Clinical grading score 0-3; symptom score 0-3 Improved self-esteem - Pt GA

d. Patients with extragenital lichen sclerosus

Titel	First author Year	Journal	Study design	Study population	Intervention	follow up	Outcome	Notes
Age 0-12 years								
Age 13-17 years								
Age 18+								

Low-dose ultraviolet A1 phototherapy for extragenital lichen sclerosus: results of a preliminary study	Kreuter 2002	J Am Acad Dermatol	Prospective	10 patients with biopsy proven LS	UVA1 4 times/ week - total 40 treatments (total doses 800 J/cm2)	1y	PGA CS (mean)pre= 7.6 (0.84), post= 2.3(0.95). Ultrasound, epidermal thickness – improved	
Efficacy of UVA1 phototherapy in 230 patients with various skin diseases	Rombold 2008	Photodermatol Photoimmunol Photomed	Retrospective	10 patients with LS	UVA1 – Total doses 1018.00 ± 575.30 J/cm2	20.7 +/-8.7 sessions	80% improved - PGA (slight 40%, moderate 30%, marked 10%)	
All ages								
Systemic immunosuppressive/immunomodulating treatment								
Methotrexate for the treatment of recalcitrant genital and extragenital lichen sclerosus: A retrospective series	Cuellar-Barboza 2020	Dermatol Ther	Case series	28 patients with LS, 24 of whom had extragenital involvement and all of whom had previously failed topical treatments	MTX (2.5-17.5 mg) median = 10 mg	No information (treatment duration ranged from 1 to 61 months (median = 8)	Initial clinical improvement: 21/28 ustained improvement: 15/28	Letter with little information, some patients used additional topical treatments

e. Mixed (without information on the localisation)

Titel	First author Year	Journal	Study design	Study population	Intervention	follow up	Outcome	Notes
Age 0-12 years								
Age 13-17 years								
Age 18+								
Others								
New: A novel technique with autologous nanofat grafting to restore tissues in lichen sclerosus genital disease	Kurti 2020	Eur. Urol. Open Sci.	Case series	6 male and 7 female patients with LS	Autologous nanofat grafting	M 10 m (range: 6-18)	Complete disappearance of pain, itching, discomfort 13/13 improve of urinary flow, quality of life and restore sexual function 13/13	Conference abstract, little information on outcomes
All ages								

Photo therapy								
New: Ultraviolet A1 phototherapy: One center's ltraviolet A1 phototherapy: One center's experience	Attili 2017	Indian J Dermatol V enereol Leprol	Retrospecti ve case series	14 patients	UVA1	No information	Benefical 6/14 no benefical 8/14	Little information on outcomes

Abbreviation list

*	ITT was created by the reviewers
black writing	new data
5-ALA	5-aminolävulin acid
AE	adverse event
bl	baseline
BMG	buccal mucosal graft
CP	clobetasol propionate
D	dyspaneuria
DLQI	Dermatology Life Quality Index
ERT	estrogen replacement therapy
FSDS	Female Sexual Distress Scale
FSFI	Female Sexual Function Index
GOS	Global Objective Score
GRA	Global Response Assessment
GSS	Global Subjective Score
HADS	Hospital Anxiety and Depression Scale
HADS	Hospital Anxiety and Depression Scale
IGA	Investigator Global Assessment
IQR	interquartile range
LS	Lichen sclerosus
LUTS	lower urinary tract symptoms
M	mean
m	month
MAL-PDT	Methyl aminolevulinate Protoporphyrin Photodynamic therapy
MD	mean difference
Mdn	median
MenLAS	male counterpart scale
mL	millilitres
MMF	mometasone furoate
mVVSQ	modiefied vulvovaginal symptoms questionnaire
MSHQ	men sexual function questionary
MTX	methotrexate
n	number of patients
n/a	not available
PASS-20	Pain Anxiety Symptoms Scale
PGA	Physician 's Global Assessment
PRISM	Pictorial Representation of Illness and Self-Measure
PRP	platelet-rich plasma
PTD	photodynamic therapy
Qmax	maximal urinary flow rate
s	second
SAE	severe adverse event
SD	standard deviation
SHAP	skin hypopigmentation area percentage
SHIM	Sexual Health Inventory for Men
TOS	total objective score
TSS	total subjective score
UV	ultraviolett
VAS	Visual Analogue Scale
VIN	vulval intraepithelial neoplasia
VLS	vulval lichen sclerosus
w	week
y	year

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