EUROGUIDERM GUIDELINE ON LICHEN SCLEROSUS– METHODS REPORT

Version 1.0, June 2023

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Notes on use/Disclaimer

This is the methods report of the evidence and consenus based EuroGuiDerm Lichen Sclerosus guideline.

Funding

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

Involving stakeholders and forming the guideline subcommittee

A direct invitation to nominate an expert to participate in the GL development was send to all EuroGuiDerm funding societies (n=15, in August 2021). In addition, the european academy paediatrics (EAP), the European board & college of obstetrics and gynaecology (EBCOG), the European Board of Urology (EBU) and the UEMS Surgery Section were each asked to nominate an expert. Also, Verein Lichen sclerosus and Lichen sclerosus Deutschland received direct invitations to nominate two patient representatives each. Unfortunately, we did not receive nominations from all the societies we approached. Additionally, an open call went out to all EDF members and was circulated via social media/newsletters. Some representatives were also nominated directly by the coordinator Gudula Kirtschig (GK).

All persons nominated received an invitation to submit their conflict of interest (COI) declaration online and to self-declare their 1) personal-financial interests (P-F) 2) non-personal financial interestes (NP-F), and 3) their personal non-financial interests (P-NF). The EuroGuiDerm Board of Directors made the final decision on which candidates may participate considering these declarations on November 2021. Experts were informed thereafter.

TABLE 1: MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP

Title	First name	Last name	Institution	Country	Speciality/Profession	Role
Prof.	Guido	Barbagli	Center for reconstructive urethral surgery, Arezzo – Italy	Italy	Urology	Co-author

Dr.	Karl	Becker	Office for Paediatric surgery, Bonn, Germany.	Germany	Paediatric surgery	Co-author
Dr.	Michael J.	Boffa	Department of Dermatology, Mater Dei Hospital, Msida, Malta.	Malta	Dermatology	Co-author
Prof.	Ching-Chi	Chi	Department of Dermatology, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan. College of Medicine, Chang Gung University, Taoyuan, Taiwan., Taoyuan, Taiwan	Taiwan	Dermatology, evidence based medicine	Co-author
Prof.	Monica	Corazza	Section of Dermatology and Infectious Diseases, Department of Medical Sciences, University of Ferrara, Ferrara, Italy.	Italy	Dermatology	Co-author
Dr.	Jean Noel	Dauendorffer	Department of Dermatology, Centre for genital and sexually transmitted diseases, University Hospital Saint Louis, Paris.	France	Dermatology	Co-author
	Bettina	Fischer	Verein Lichen Sclerosus	Switzerland	Patient representative	Co-author
Prof.	Andreas	Günthert	Department of Gynecology, Lucerne Cantonal Hospital, Lucerne, Switzerland.	Switzerland	Gynaecology	Co-author
Prof.	Eija	Hiltunen-Back	Department of Dermatovenereology, Helsinki University Hospital, Helsinki, Finland	Finland	Dermatology	Co-author
	Alexander	Höfinger	Verein Lichen Sclerosus	Austria	Patient representative	Co-author
Prof.	Helle Kiellberg-	Larsen	Department of Dermatology and Venereology, Copenhagen University Hospital, Bispebjerg Hospital, Copenhagen, Denmark.	Denmark	Dermatology	Co-author
PD Dr.	Gudula	Kirtschig	Medbase Health Centre, Frauenfeld, Switzerland.	Germany	Dermatology	Coordinator and co-author
	Narayani Helga	Köllmann	Verein Lichen sclerosus	Switzerland	Patient representative	Co-author
Prof.	Alexander	Kreuter	Department of Dermatology, Venereology, and Allergology, HELIOS St. Elisabeth Hospital Oberhausen, Oberhausen, Germany.	Germany	Dermatology	Co-author
	Herta	Kühn	Lichen Sclerosus Deutschland e.V.	Germany	Patient representative	Co-author
Dr.	Massimo	Lazzeri	Department of Urology, IRCCS Humanitas Research Hospital, Rozzano (MI), Italy.	Italy	Urology	Co-author
Prof.	Werner	Mendling	German Center for Infections in Gynecology and Obstetrics, at Helios University Hospital Wuppertal– University Witten/Herdecke, Germany	Germany	Gynaecology	Co-author
PD Dr.	Simon	Müller	Department of Dermatology, University Hospital Basel, Basel, Switzerland	Switzerland	Dermatology	Co-author
Prof.	Arjen F.	Nikkels	Department of Dermatology, University Medical Center of Liège, Liège, Belgium.	Belgium	Dermatology	Co-author
Dr.	Martin	Promm	Department of Paediatric Urology and Clinic St. Hedwig, University Medical Centre of Regensburg, Regensburg, Germany.	Germany	Urology	Co-author
Prof.	Kristin Katharina	Rall	Department of Women's Health, Women's University Hospital Tuebingen, Tuebingen, Germany.	Germany	Gynaecology	Co-author

Dr.	Marjo	Ramakers	CenSeRe (Centre for Psychological, Relational, Sexual Health), Voorschoten, the Netherlands	Netherlands	Sexulogy	Co-author
Prof.	Sigrid	Regauer	Diagnostic and Research Institute of Pathology, Medical University Graz, Graz, Austria.	Austria	Histopathology	Co-author
Prof.	Miklós	Sárdy	Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary.	Hungary	Dermatology	Co-author
Prof.	Norbert	Sepp	Department of Dermatology and Venereology, Ordensklinikum Linz Elisabethinen, Linz, Austria.	Austria	Dermatology	Co-author
Dr.	Rosalind	Simpson	Centre of Evidence Based Dermatology, University of Nottingham, Nottingham, UK.	United Kingdom	Dermatology	Co-author
Prof.	Raimund	Stein	Center for Pediatric, Adolescent and Reconstructive Urology, Medical Faculty Mannheim, University of Medical Center Mannheim, Heidelberg University, Mannheim, Germany.	Germany	Urology	Co-author
Dr.	Turid	Thune	Department of Dermatology, Haukeland University Hospital, Bergen, Norway.	Norway	Dermatology	Co-author
Dr.	Aikaterini	Tsiogka	National and Kapodistrian University of Athens, Faculty of Medicine, 1st Department of Dermatology-Venereology, Andreas Sygros Hospital, Athens, Greece.	Greece	Dermatology	Co-author
Dr.	Colette	Van Hees	Department of Dermatology, Erasmus University Medical Center, Rotterdam, the Netherlands.	The Netherlands	Dermatology	Co-author
Prof.	Snejina	Vassileva	Department of Dermatology and Venereology, University Hospital "Alexandrovska", Medical University - Sofia, Sofia, Bulgaria.	Bulgaria	Dermatology	Co-author
	Suzanne	Von Seitzberg	Danish Association for Lichen Sclerosus	Denmark	Patient representative	Co-author
	Lena	Voswinkel	Lichen sclerosus Deutschland e.V.	Germany	Mother of a patient	Co-author
Prof.	Linn	Wölber	Department of Gynaecology, University Medical Centre Hamburg-Eppendorf and Centre for Colposcopy and Vulvovaginal disease Jersualem Hospital Hamburg, Hamburg, Germany.	Germany	Gynaecology	Co-author
Methodologists:						
	Martin	Dittmann	Division of Evidence Based Medicine (dEBM), Charité - Universitätsmedizin Berlin	Germany	Information specialist	Team support, information specialist
	Matthew	Gaskins	Division of Evidence Based Medicine (dEBM), Charité - Universitätsmedizin Berlin	Germany	Systematic review methods	Methodologist
Dr.	Maria	Kinberger	Division of Evidence Based Medicine (dEBM), Charité - Universitätsmedizin Berlin	Germany	Systematic review methods	MD, Methodologist

Prof.	Alexander	Nast	Division of Evidence Based Medicine (dEBM), Charité - Universitätsmedizin Berlin	Germany	Systematic review methods; certified guideline facilitator	MD, Methodologist: Director EuroGuiDerm
PD Dr.	Ricardo N.	Werner	Division of Evidence Based Medicine (dEBM), Charité - Universitätsmedizin Berlin	Germany	Systematic review methods; certified guideline facilitator	MD, Methodologist

Declaration and management of conflicts of interest

Experts were asked self-declare their interests as describes above via the online tool: ***Declaration of Interests for EuroGuiDerm Guidelines*** online (http://ask.debm.de/index.php/981542?lang=en).

In line with the EuroGuiDerm Methods Manual, all experts can take part in the discussion. However, declaring personal-financial interests means that the person is not eligible to vote on recommendations. Of the 34 members of the guideline development group (GDG), 0 % (n=0) reported having personal-financial interests.

Scoping and defining the purpose of the guideline

The EuroGuiDerm team (MK and RNW) and the guideline coordinator (GK) prepared a scoping document. The manuscript was sent to the EDF members and the EuroGuiDerm Board of Directors in November 2021 for commenting and approval, see Appendix 3.

This guideline is an update of the evidence and consensus-based European guideline for Lichen Sclerosus published in 2016. The guideline coordinator (GK) and the EuroGuiDerm team (MK and RNW) developed the structure of the guidelines and formulated key questions for each chapter, considering the topics covered in the previous guideline as well as new areas. All key questions were presented to the GDG during the first online conference (kick off) on 06 December 2021 and all GDG members could modifiy key question(s) for their assigned topic(s)/chapter(s) if required.

TABLE 2: OVERVIEW OF KEY QUESTIONS AND CHAPTER CONTENT

Chapter	Key-Question(s) or content
Introduction	Definition of disease, histopathology, genetic predisposition, immunological findings, associated diseases
Epidemiology	Epidemiology of lichen sclerosus (sex, age, ethnicity)
Clinical presentation	Clinical presentation of lichen sclerosus: signs and symptoms depending on site and sex
Sequel of disease	Scarring, development of carcinomas
Trigger factors	Potential trigger factors for lichen sclerosus
Diagnostic	What is the best diagnostic algorithm for male and female lichen sclerosus patients in different age groups? When, where and how should a sample biopsy be taken?

	Should routine diagnostic measures be performed to identify potentially associated diseases?
Differential diagnoses	Main differential diagnoses
Introduction into treatment	What are the aims of treatment? How should treatment success be assessed and how often should patients be seen? What schemes can be recommended for initial and maintenance treatment?
Skin care and basic therapy	Skin care, avoidance of trigger factors and prevention contact allergy, treatment of itch
Emollients	**What is the efficacy and safety of emollients in patients with genital lichen sclerosus?***
Topical and intralesional corticosteroids	**What is the efficacy and safety of topical and intralesional corticosteroids in patients with genital lichen sclerosus?***
Topical calcineurin inhibitors	**What is the efficacy and safety of topical calcineurin inhibitors in patients with genital lichen sclerosus?***
Topical retinoids	**What is the efficacy and safety of topical retinoids in patients with genital lichen sclerosus?***
Topical hormone preparations	**What is the efficacy and safety of topical hormone preparations in patients with genital lichen sclerosus?***
Platelet rich plasma	**What is the efficacy and safety of platelet rich plasma in patients with genital lichen sclerosus?***
UV therapy	**What is the efficacy and safety of UV therapy in patients with genital lichen sclerosus?***
Photodynamic therapy	**What is the efficacy and safety of photodynamic therapy in patients with genital lichen sclerosus?***
Laser therapy	**What is the efficacy and safety of laser therapy in patients with genital lichen sclerosus?***
Cryotherapy	**What is the efficacy and safety of cryotherapy in patients with genital lichen sclerosus?***
Systemic treatment	**What is the efficacy and safety of systemic immunosuppressive treatment in patients with genital lichen sclerosus?***
Surgical interventions	**Which surgical interventions are available for female and male patients with genital lichen sclerosus?**
Upcoming treatments	What treatments are currently under development
Extragenital lichen sclerosus	**Features of extragenital lichen sclerosus**
Patient education programs	Are effective patient education programmes available? If so, what is effective patient education?
Lichen sclerosus in pregnancy	How does lichen sclerosus behave during pregnancy? **How should lichen sclerosus be treated during pregnancy?**
Pain in lichen sclerosus**	Chronic pelvic pain syndrome / vulvodynia in LS patients, treatment for pain in lichen sclerosus patients
Follow-up	How often should patients with lichen sclerosus attend follow-up examinations?

	What does follow-up entail in patients with lichen sclerosus? (clinical examination, patient education and frequency)
Interdisciplinary mangagement	When should patients be seen by an interdisciplinary senario / team? What are the advantages or disadvantages of interdisciplinary clinics? (e.g. outcomes, patient experience, micro and macro economic considerations)
Improvement of care	Triage (escalation of care: Gp / local specialist / speicialised physician / interdisciplinary team) / LS centres, physician location map
Future research	Urgent research questions, COS development
*analyses will be stratified for age groups, sex and site of involvement ** The addition of this chapter was decided during the first consensus conference (not at the kick-off meeting) **evidence-based questions in bold**	

After evaluating the evidence, it was found that for some chapters, which were initially planned to have evidence-based recommendations, only consensus-based recommendations could be made as the data was insufficient for evidence-based decisions. These chapters include emollients, surgical interventions, and lichen sclerosus in pregnancy.

Search methods and results, evidence selection & critical appraisal of evidence

As part of the scoping exercise, we searched in the Guidelines International Network (G-I-N), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), ECRI Guidelines Trust, Association of the Scientific Medical Societies (AWMF) and PubMed databases for existing lichen sclerosus guidelines published during the last 5 years. We identified 14 guidelines, each of which we assessed using the Agree 2 tool (domain 3 only). The British lichen sclerosus guideline published in 2018[1] received the highest rating of 90% (see appendix 3). Consequently, we decided to utilize the systematic review from this guideline as the foundation for our own guideline. We thank the British Association of Dermatologists (BAD) for providing the data from their systematic review. They kindly allowed us to utilize and update this data, which formed the evidence base for this guideline.

Given that we adopted a narrower PICO definition than the UK guideline (see evidence report), some studies included in the systematic review of the UK guideline were excluded from the systematic review for our guideline. The following studies were excluded:

- Ayhan 2007[2]: As this was a retrospective study, we have included it only in the descriptive analysis
- D'Antuono 2011[3]: This study was not included in our update because dermasilk is not included in our PICO
- Wilkinson 2012[4]: As this was a retrospective study, we have included it only in the descriptive analysis
- Goldstein 2015[5]: This study was not included in our update because human fibroblast lysate cream is not included in our PICO

We conducted a systematic literature up-date search in the databases Pubmed, Medline Ovid from 1946, Embase Ovid from 1974 and the Cochrane database. The search strategies from the British

guideline were used (see Appendix 4). The search was running on 9 September 2021 for the period 2017 to 9 September 2021.

Two members of the EuroGuiDerm team (MK and MG) independently screened all identified abstracts/titles for eligibility. Included title/abstracts were then independently screened as full texts based on the eligibility criteria. Disagreement in evaluation was resolved through discussion by each step. The study selection flowchart is shown below. We recorded all full-texts excluded and the primary reason for exclusion (see below).

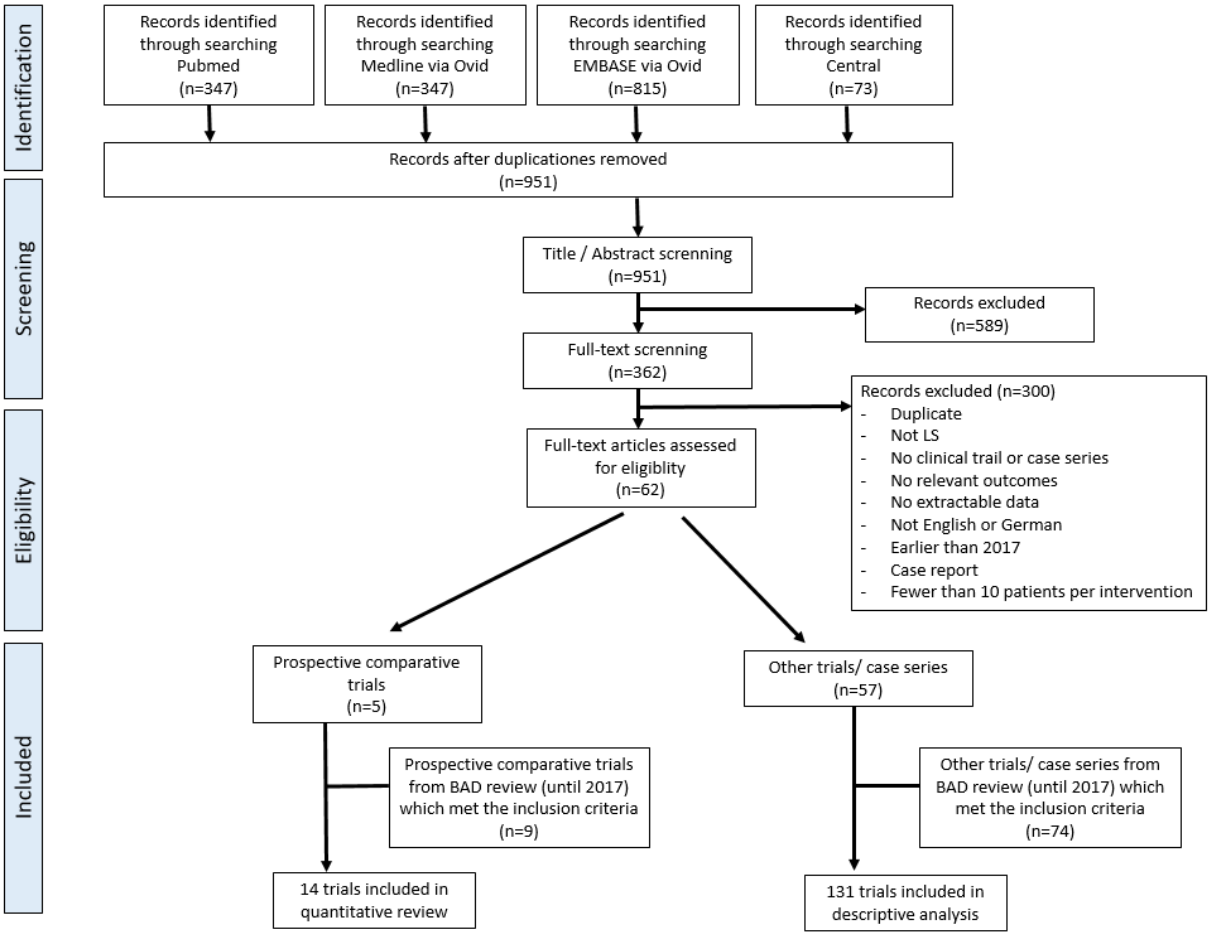

FIGURE 1: study selection flowchart

TABLE 3: EXCLUDED FULL-TEXTS FOR THE REVIEW

First author	Publication year	Reason for exclusion
Pekala, K. R.	2019	no extractable data
Ness, D.	2017	no relevant outcomes
Nct	2006	earlier than 2017

Murphy, D.	2002	earlier than 2017
Kohn, J.	2018	duplicate
Haefner, H. K.	2019	no clinical trail
Doiron, P. R.	2017	no extractable data
Declercq, A.	2020	no clinical trail
Das, R. K.	2017	no extractable data
Cocci, A.	2019	not LS
Bizjak-Ogrinc, U.	2017	duplicate
Balakirski, G.	2021	no relevant outcomes
Arena, S.	2017	no clinical trail
Zumstein, V.	2020	no relevant outcomes
Zumrutbas, A.	2019	no extractable data
Zierz, P.	1960	earlier than 2017
Zellis, S.	1996	earlier than 2017
Zeller, S.	2018	no clinical trail
R. B. R. z85rcz	2021	trail protocol
Yordanov, A.	2021	<10 patients per intervention
Yap, T.	2015	earlier than 2017
Yap, J.	2018	not LS
Yalici-Armagan, B.	2021	no extractable data
Woelber, L.	2020	no clinical trail
Wijaya, M.	2021	duplicate
Wang, M.	2020	duplicate
Wallace, S. L.	2020	no extractable data
Vittrup, G.	2021	No treatment
Vittrup, G.	2019	duplicate
Vittrup, G.	2019	duplicate
Virgili, A.	2020	no extractable data
Viers, B. R.	2017	no extractable data
Viers, B. R.	2017	no extractable data
Vassudeo, V.	2020	no extractable data

Van Hees, C. L. M.	2012	earlier than 2017
Van Der Avoort, I.	2012	earlier than 2017
van Cranenburgh, O. D.	2017	no extractable data
Usupbaev, A. C.	2021	no extractable data
Torres, S. B.	2019	no treatment
Tesdahl, B.	2017	no extractable data
Teovska Mitrevska, N.	2019	no extractable data
Tedesco, M.	2020	no extractable data
Tedesco, M.	2020	duplicate
Tausch, T. J.	2015	earlier than 2017
Talab, S. S.	2019	no extractable data
Szakos, E.	2019	no extractable data
Sultan, M.	2016	earlier than 2017
Sultan, M.	2017	no relevant outcomes
Subhadarshani, S. Khanna, N.	2020	no treatment
Stehr, M.	2019	no extractable data
Sridhar, P.	2017	no extractable data
Spilotros, M.	2019	no clinical trail
Spekreijse, J. J.	2020	no extractable data
Solopova, A. G.	2019	not in English or German
Solopova, A. G.	2021	not in English or German
Solopova, A. G.	2020	not in English or German
Snodgrass, W.	2017	<10 patients per intervention
Skrodzka, M.	2018	no extractable data
Singh, L.	2018	no relevant outcomes
Sharova, A.	2019	no LS
Sharova, A.	2019	duplicate
Shah, M.	2021	no treatment
Shah, M.	2020	no treatment
Shah, M.	2017	no treatment
Sekiguchi, Y.	2019	no LS

Sekiguchi, Y.	2019	no LS
Sauder, M. B.	2014	earlier than 2017
Satyagraha, P.	2016	earlier than 2017
Satyagraha, P.	2016	earlier than 2017
Satmary, W.	2018	no LS
Satmary, W.	2017	no LS
Sakurai, H.	2018	no extractable data
Russo, T.	2019	no relevant outcomes
Ruiz-Grana, S.	2021	no extractable data
Rozanski, A.	2020	no extractable data
Roberts, J. N. T.	2020	no LS
Roberts, J.	2021	no LS
Rees, S.	2019	no treatment
Ranum, A.	2021	case report
Promm, M.	2020	no clinical trail
Preto, M.	2020	duplicate
Preto, M.	2020	duplicate
Preto, M.	2020	duplicate
Preto, M.	2021	no extractable data
Prasad, S.	2020	no clinical trail
Pounds, R.	2018	no LS
Potts, B. A.	2016	earlier than 2017
Posey, L. K.	2017	duplicate
Polonia-Valente, R.	2019	no treatment
Poladi, S.	2019	no extractable data
Pniewski, T.	2016	earlier than 2017
Plachouri, K. M.	2021	case report
Pinelli, S.	2017	case report
Pineiro, M. L.	2020	no extractable data
Pineiro, M. L.	2019	no extractable data
Pfistermuller, K. L.	2017	no LS
Petersen, E. E.	2016	earlier than 2017

Pergialiotis, V.	2020	duplicate
Pergialiotis, V.	2020	no relevant outcomes
Perez-Lopez, F.	2016	no extractable data
Perdzyński, W.	2020	<10 patients per intervention
Payne, S. R.	2020	no relevant outcomes
Payne, S. R.	2018	no relevant outcomes
Payne, S. R.	2018	no relevant outcomes
Park, S. H.	2019	no relevant outcomes
Pardeshi, A.	2017	no extractable data
Pagano, R.	2016	earlier than 2017
R. B. R. p9s5y	2019	trial protocol
Osminina, M. K.	2020	<10 patients per intervention
Nichols, A. E.	2015	earlier than 2017
Nic Dhonncha, E.	2021	no relevant outcomes
Nic Dhonncha, E.	2020	no relevant outcomes
Nguyen, Y.	2018	duplicate
Nguyen, Y.	2018	duplicate
Nguyen, Y.	2018	duplicate
Nguyen, Y.	2018	no relevant outcomes
Nguyen, Y.	2017	duplicate
Nerantzoulis, I.	2017	no extractable data
Nct,	2021	no results
Nct,	2021	no results
Nct,	2021	no results
Nct,	2019	no results
Nct,	2019	no results
Nct,	2019	no results
Nct,	2018	no intervention
Nct,	2018	duplicate
Nct,	2017	duplicate
Nct,	2016	earlier than 2017
Nct,	2015	earlier than 2017

Nct,	2011	earlier than 2017
Nct,	2010	earlier than 2017
Nct,	2008	earlier than 2017
Nathwani, P. M.	2017	no relevant outcomes
D. I. Meo N.	2018	no extractable data
Mundy, A.	2019	no extractable data
Morrel, B.	2020	no clinical trail
Morey, A. F.	2017	no clinical trail
Monn, M. F.	2019	no extractable data
Monn, M. F.	2020	no extractable data
Modgil, V.	2015	earlier than 2017
Mendling, W.	2020	duplicate
Mendling, W.	2019	no clinical trail
Mendieta-Eckert, M.	2017	case report
Melnick, L. E.	2020	no relevant outcome
Meani, R.	2017	no treatment
McClatchey, T.	2017	no extractable data
Mazzoni, D.	2021	no relevant outcomes
Mazdziarz, A.	2019	<10 patients per intervention
Mautz, T. T.	2021	no clinical trail
Mauskar, M. M.	2021	no clinical trail
Mashayekhi, S.	2017	no clinical trail
Martinez, M. J.	2019	no extractable data
Marnach, M. L.	2021	no clinical trail
Manukhin, I. B.	2021	not in English or German
Mangir, N.	2020	no extractable data
Liu, J.	2021	duplicate
Liu, J.	2018	no extractable data
Li, H. O. Y.	2021	duplicate
Li, H. O. Y.	2021	duplicate
Li, C.	2015	earlier than 2017

Lee, A.	2015	earlier than 2017
Lee, A.	2015	earlier than 2017
Le, S. T.	2018	no relevant outcomes
Lavoie, C.	2018	no relevant outcomes
Kwok, M.	2019	no relevant outcomes
Kurtzman, J. T.	2021	duplicate
Kurtzman, J. T.	2021	no extractable data
Krychman, M.	2016	earlier than 2017
Krychman, M.	2017	no relevant outcomes
Krychman, M.	2017	no relevant outcomes
Kravvas, G.	2018	no relevant outcomes
Kravvas, G.	2020	no LS
Kozak, U.	2020	no LS
Kohn, J. R.	2018	no extractable data
Kohn, J.	2019	no extractable data
King, C.	2019	no relevant outcomes
Kerr, L.	2020	no relevant outcomes
Kato, T.	2018	no relevant outcomes
Kasprowicz-Furmanczyk, M.	2020	no extractable data
Karadag, A. S.	2018	<10 patients per intervention
Kammire, M. S.	2021	no extractable data
Kamilos, M. F.	2021	no extractable data
Kakko, T.	2018	no relevant outcomes
Jun, M. S.	2018	no extractable data
Joshi, S.	2016	earlier than 2017
Jeffery, N.	2020	no extractable data
Isrctn,	2017	trail protocol
Ismail, D.	2018	duplicate
Hyams, M. N.	1950	earlier than 2017
Hughes, K. E.	2020	no relevant outcomes
Horiguchi, A.	2017	no clinical trail

Hong, M.	2017	no extractable data
Hilton, P. A.	2019	no treatment
Harvey, G.	2018	no LS
Harmon, M. L.	2017	no clinical trail
Hampl, M.	2019	no clinical trail
Hakenberg, O. W.	2018	no LS
Hagerman, G. F.	2019	no clinical trail
Guo, H.	2018	no LS
Gujral, S.	2019	case report
Guidozzi, F.	2021	duplicate
Guidozzi, F.	2021	no clinical trail
Griffin, M. F.	2017	no clinical trail
Green, P. A.	1019	no relevant outcomes
Gomella, A.	2017	no relevant outcomes
Goldstein, A.	2019	duplicate
Gkouvi, A.	2020	duplicate
Gkouvi, A.	2020	case report
Ghidini, F.	2021	no relevant outcomes
Gardner, A.	2020	no extractable data
Gandhi, A. B.	2018	no extractable data
Gambelli, I.	2017	duplicate
Gajewska, M.	2018	<10 patients per intervention
Folaranmi, S. E.	2018	no relevant outcomes
Fersovich, J.	2020	no extractable data
Ferrara, F.	2020	duplicate
Ferrara, F.	2020	duplicate
Ferrara, F.	2020	no extractable data
Fergus, K. B.	2020	no treatment
Fahy, C. M. R.	2017	no relevant outcomes
Eva, L.	2018	no LS
Euctr, N. L.	2011	earlier than 2017
Euctr, N. L.	2007	earlier than 2017

Euctr, N. L.	2017	trail protocol
Eshtiaghi, P.	2019	no clinical trail
Elias, J.	2018	no extractable data
Dobson, J.	2017	no extractable data
Di Meo, N.	2018	no extractable data
Di Lellis, M. A.	2021	no extractable data
Di Altobrando, A.	2021	<10 patients per intervention
DeLong, J.	2017	no LS
Dell, E. A.	2018	no extractable data
Dell, E.	2018	no LS
De Magnis, A.	2019	no LS
De Belilovsky, C.	2020	duplicate
De Belilovsky, C.	2019	duplicate
Day, T.	2015	earlier than 2017
Day, T.	2018	no LS
Day, T.	2017	duplicate
Day, T.	2021	no treatment
Day, T.	2017	no treatment
Daneshvar, M.	2020	no LS
Daneshvar, M.	2018	no LS
Curro, M.	2018	no relevant outcomes
Coyle, M.	2018	<10 patients per intervention
Corazza, M.	2020	no extractable data
Corazza, M.	2018	duplicate
Corazza, M.	2019	no treatment
Chung, A. S. J.	2020	no extractable data
Chmel, R.	2019	<10 patients per intervention
ChiCtr,	2020	trial protocol
Chi, C. C.	2011	earlier than 2017
Cheng, H. S.	2020	no treatment
Cheng, H. S.	2017	no treatment

Catton, K.	2018	no relevant outcomes
Campos-Juanatey, F.	2020	no extractable data
Calopedos, R.	2019	no relevant outcomes
Burkett, L.	2020	duplicate
Burger, M. P. M.	2015	earlier than 2017
Brunn, E.	2018	no extractable data
Bratila, E.	2017	no extractable data
Bradford, J.	2015	earlier than 2017
Borghi, A.	2018	no extractable data
Borghi, A.	2021	no clinical trail
Bizon-Szpernalowska, M.	2020	no extractable data
Bizjak-Ogrinc, U.	2018	duplicate
Bevans, S. L.	2017	no clinical trail
Betancourth-Alvarenga, J. E.	2017	no relevant outcomes
Benson, C. R.	2021	no extractable data
Benson, C. R.	2019	duplicate
Ben-Aroya, Z.	2015	earlier than 2017
Belotto, R. A.	2017	duplicate
Belotto, R. A.	2017	trial protocol
Belotto, R.	2018	no relevant outcomes
Bekkema, J.	2019	no extractable data
Beamer, M.	2020	duplicate
Athota, K.	2020	no relevant outcomes
Ashley, S.	2020	no extractable data
Anonymous,	2019	no extractable data
Anonymous,	2019	no extractable data
Angulo, J. C.	2017	not in English or German
Anemuller, W.	2016	earlier than 2017
Alyami, F. A.	2018	no relevant outcomes
Almadori, A.	2017	no extractable data
Alaniz, V. I.	2019	case report

Akbas, A.	2021	no relevant outcomes
Actrn,	2018	trial protocol
Chernova, N. I.	2020	not in English or German
Maretti, C.	2018	no extractable data
Levy, A.	2019	no extractable data
Leganes Villanueva, C.	2020	no extractable data
Kohn, J. R.	2020	no extractable data
Ismail, D.	2019	no relevant outcomes
Hayden, J. P.	2020	no extractable data
Chin, S.	2020	no LS
Chapman, D.	2020	no extractable data
Chapman, D.	2020	no extractable data
Balakirski, G.	2020	no extractable data

Data extraction was also performed independently by two members of the EuroGuiDerm team (MK and MG) using a standardised form. A table was created for all prospective comparative trails (randomised controlled trials and prospective comparative observational studies) and another table for case series and non-prospective trials. The data presented in the second table, which included case series and non-prospective studies, were solely described and not subjected to further analysis. Disagreement in evaluation was resolved through discussion by each step.

To assess risk of bias in randomized trials we used the RoB 2.0 tool.[6] This was also evaluated by the two members of the EuroGuiDerm team (MK and MG) independently. The RCTs that were already included in the systematic review of the 2018 UK guideline were still assessed with the first risk of bias tool. For comparative prospective observational studies, the assessment of risk of bias was planned with the ROBINS-1 tool. However, no new comparative prospective observational studies were included. Disagreement in evaluation was resolved through discussion.

After comparison of the extracted data between the two independent reviewers, the data oft the prospective comparative trails was transferred and further processed using the Review Manager (RevMan) 5.3 software.

Fixed-effects (Mantel-Haenszel) techniques (using an inverse variance method for pooling) were used to calculate the risk ratios (RR) for dichotomous outcomes. Mean differences (MD) were calculated for continuous outcomes.

We had intended to conduct a meta-analysis by pooling data from different trials wherever possible. However, due to the heterogeneity in comparisons and outcomes, this was never feasible.

To assess the certainty of the evidence on the outcomes from the prospective comparative trails we used the "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach.[7] Each outcome was examined for each of the quality elements listed and defined in Table 4.

TABLE 4: DESCRIPTION OF QUALITY ELEMENTS IN GRADE FOR INTERVENTION STUDIES

Quality element	Description
Risk of bias *(i.e. study limitations)*	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect. Examples of such limitations are selection bias (often due to poor allocation concealment), performance and detection bias (often due to a lack of blinding of the patient, healthcare professional and assessor) and attrition bias (due to missing data causing systematic bias in the analysis).
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of effect estimates between studies in the same meta-analysis.
Imprecision	Results are imprecise when studies include relatively few patients and few events (or highly variable measures) and thus have wide confidence intervals around the estimate of the effect relative to clinically important thresholds. The 95% confidence intervals denote the possible range of locations of the true population effect at a 95% probability, and so wide confidence intervals may denote a result that is consistent with conflicting interpretations (for example, a result may be consistent with both clinical benefit AND clinical harm) and thus, be imprecise.
Publication bias	Publication bias is a systematic under/overestimation of the underlying beneficial or harmful effect due to the selective publication of studies. A closely related phenomenon is where some papers fail to report an outcome that is inconclusive, thus leading to an over-estimate of the effectiveness of that outcome.
Other issues	Sometimes, randomization may not adequately lead to group equivalence of confounders, and if so this may lead to bias, which should be considered. Potential conflicts of interest, often caused by excessive pharmaceutical company involvement in the publication of a study, should also be noted.

Table adapted from: Lewis et al., 2018, Appendix K [8]

The rating of the quality of evidence begins with the study design. For outcomes from RCTs, the baseline GRADE evidence quality score is set to "high." Outcomes from observational intervention studies, on the other hand, are initially assessed as "low". After that, the rating is done for domains "inconsistency", "indirectness", "imprecision" and "publication bias". Depending on these ratings the quality of evidence can be subsequently downgraded. Table 5 shows the criteria for downgrading.

TABLE 5: CRITERIA FOR DOWNGRADING THE CONFIDENCE IN THE EFFECT ESTIMATORS

Quality element	Criteria	Effect on the GRADE rating
Risk of bias	Low – moderate	No downgrading
	High in one domain	Downgrading -1
	High in more than one domain	Downgrading -2
Inconsistency	Only one contributing study	No downgrading
	More than one contributing study	
	• I^2 was 0-49%	No downgrading
	• I^2 was 50-74%	Downgrading -1
	• I^2 was 75% or more	Downgrading -2
	• subgroup analysis (each subgroup had an $I^2 < 50$)	No downgrading
Indirectness	Evaluation of indirectness in populations, interventions, comparisons and outcome measures	
	• No indirectness	No downgrading
	• Indirectness in just one source	Downgrading -1
	• Indirectness in more than one source	Downgrading -2
Imprecision	Categorical/dichotomous outcomes In absence of minimal important differences (MID) values, MIDs are taken as risk ratios (RRs) of 0.75 and 1.25	
	• 95% confidence interval of the overall estimate of effect does not crossed the MID lines	No downgrading
	• If 95% confidence interval of the overall estimate of effect crossed one of the MID lines	Downgrading -1
	• If 95% confidence interval of the overall estimate of effect crossed both of the MID lines	Downgrading -2
	Countinous outcomes	

	In absence of MID values, MIDs are taken as ½ standard deviation oft he control group	
	• 95% confidence interval of the overall estimate of effect does not crossed the MID lines	No downgrading
	• If 95% confidence interval of the overall estimate of effect crossed one of the MID lines	Downgrading -1
	• If 95% confidence interval of the overall estimate of effect crossed both of the MID lines	Downgrading -2
Publication bias	Not detectable	No downgrading
	Detected (e.g. with funnel plot)	Downgrading -1

As it was not feasible to pool the data due to the small number of studies and their heterogeneity, no downgrading was performed for the domains of 'inconsistency' and 'publication bias'. Since the study inclusion criteria already prevented indirectness, no downgrading was necessary in this domain either. An upgrading is possible if there is a large effect, a dose response or plausible confounding bias. However, this was not the case here, so that no upgrading took place.

For the evidence analysis see evidence report.

Developing background texts

During the online kick-off meeting, the distribution of tasks was discussed and documented, see Table . Afterwards, the author groups received chapter templates and work out the background texts.

TABLE 6: DISTRIBUTION OF TASKS

Chapter	Authors
Introduction	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall
Epidemiology	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Becker
Clinical presentation	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Becker
Sequel of disease	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Becker
Trigger factors	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Becker
Diagnostic	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Wölber, Corazza, van Hees, Becker
Differential diagnoses	Kirtschig, Simpson, Sepp, Regauer, Promm, Fischer, Rall, Boffa
Introduction into treatment	Müller, Köllmann, von Seitzberg, Nikkles, Rall
Skin care and basic therapy	Boffa, Corazza, Tsiogka, Kiellberg Larsen
Emollients	Müller, Hiltunen-Back

Topical and intralesional corticosteroids	Chi, Vassileva, Nikkles
Topical calcineurin inhibitors	Chi, Vassileva, Nikkles
Topical retinoids	Corazza, Günthert
Topical hormone preparations	Günthert, Wölber, Boffa
Platelet rich plasma	EbM-Team
UV therapy	Kreuter
Photodynamic therapy	Kreuter, Corazza
Laser therapy	Höfinger, Kühn, Dauendorffer, Wölber
Cryotherapy	Kreuter
Systemic treatment	Miklos, Müller, van Hees
Surgical interventions	Barbagli, Becker, Günthert, van Hees, Fischer, Köllmann, Höfinger, Stein, Lazzeri
Upcoming treatments	Müller, Kirtschig
Extragenital lichen sclerosus	Corazza, Kreuter
Patient education programs	Seitzberg, Köllmann, Ramakers
Lichen sclerosus in pregnancy	Fischer, Tsigka, Günthert
Pain in LS*	van Hees, Ramakers
Follow-up	Kiellberg Larsen, Stein
Interdisciplinary mangagement	Müller, Kirtschig, Rall, Promm, Stein
Improvement of care	von Seitzberg, Voßwinkel, Kirtschig
Future research	von Seitzberg, Müller, Kirtschig
** The addition of this chapter was decided during the first consensus conference (not at the kick-off meeting)	

The co-authors prepared draft chapters some with and some without recommendations, which was subsequently reviewed and commented on by the EuroGuiDerm team and by GK. Following that, the co-authors revised the drafts where needed.

Developing recommendations and the consensus process

In accordance with the EuroGuiDerm Manual, we used phrasing suggested by the GRADE Working Group to standardize the wording of all recommendations.[9] This is reported as show in table 7. The strength of the consensus is also reported. Recommendations and texts were discussed and voted upon until a majority of more than 50% agreed.

TABLE 7: WORDING OF RECOMMENDATIONS [10-13]

Strength	Wording	Symbols	Implications
Strong recommendation **for** the use of an intervention	'We **recommend** . . .'	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Weak recommendation **for** the use of an intervention	'We **suggest** . . .'	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
No recommendation with respect to an intervention	'We **cannot make a recommendation** with respect to . . .'	**0**	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g. no reliable evidence data available, conflicting outcomes, etc.)
Weak recommendation **against** the use of an intervention	'We **suggest against** . . .'	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation **against** the use of an intervention	'We **recommend against** . . .'	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

Online pre-voting

Between April 2022 and November 2022 a total of 5 online pre-votings took place to (a) familiarise the group with all draft recommendations and the background texts, to (b) collect feedback from the entire group and (c) to collect a vote on the recommendations. For the online pre-voting we used the tool LimeSurvey. While completing the survey, the answers and comments of the others were not visible to those working through the survey.

The chapters were presented to all members of the guideline development group. Each member had the opportunity to agree or disagree with the draft text. In case of disagreement, the experts had the opportunity to comment or to suggest changes. All comments were reviewed by GK and the EuroGuiDerm team and all feedback was sent to the chapter authors.

The GDG members also voted on the draft recommendations and were specifically asked whether they agree or disagree with the strength and the wording of the recommendation(s). In case of disagreement, again, alternative suggestions and comments could be submitted. Although the EuroGuiDerm team could see how each person voted on the recommendations, this was never shared with the GDG. Submitted comments and suggestions were shared with the group. Comments and suggestions were not anonymised.

The results and feedback from the online surveys were then presented to the experts in the consensus conferences. If GK, the EuroGuiDerm team or the co-authors, who had developed the drafts, had adjusted the recommendations based on the survey results, the changes were presented to the experts transparently.

Consensus conferences

Three online consensus conferences took place on 15 August 2022, 22 November 2022 and 23 January 2023. Ricardo N. Werner, certified guideline facilitator, managed the process.

We used the nominal group technique[14]: Ricardo N. Werner first presented the anonymised results, comments and any suggested changes from the pre-voting surveys.

He then opened the floor for discussion. Benefits, harms, processes and procedures were extensively discussed. After the discussion, the final voting took place. The experts could ‘agree’, ‘disagree’ or ‘abstain’ for each vote. If 100% agreement was achieved in the prevoting and there was no need for further discussion, the result from the prevoting was adopted instead of another vote.

The fourth recommendation (frenuloplasty recommendation in men) in the chapter 'surgical interventions' was revised after the 3rd consensus conference to align it with the 6th recommendation of the chapter (frenuloplasty recommendation in boys). The change was voted on through an online survey via Lyme survey. The change received 100% approval.

In the guideline itself, the strength of the consensus reached for each recommendation is reported as shown in **Fehler! Verweisquelle konnte nicht gefunden werden.**.

TABLE 2: STRENGTH OF CONSENSUS

100 % consensus	100% agreement	
Strong consensus	Agreement of >95% - < 100% participants	
Consensus	Agreement of >75-95% participants	

Agreement of the majority	Agreement of >50-75% participants	

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

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

[1]1 Abstention

Ultrapotent topical corticosteroids:
Direct evidence available for:

- Women:
  - Cochrane review (2 RCTs)
  - 5 further RCTs
    - Improvement of symptoms: GRADE ⊕⊕⊕⊕ high - ⊕◯◯◯ very low
    - QoL: GRADE ⊕⊕⊕◯ moderate - ⊕⊕◯◯ low
    - Sexual function: GRADE ⊕◯◯◯ very low
    - Urinary function: GRADE ⊕⊕◯◯ low
    - Patient global assessment: GRADE ⊕⊕◯◯ low
    - Physician global assessment: GRADE ⊕◯◯◯ very low
    - Minor adverse events: GRADE ⊕◯◯◯ very low
  - 9 non-comparative/non-prospective studies (n=513)
- Girls
  - 7 non-comparative/non-prospective studies (n=155)

- Women and girls:
  - 1 RCT
    - Improvement of symptoms: GRADE ⊕⊕⊕◯ moderate
- Females age unknown:
  - 1 non-comparative/non-prospective study (n=59)
- Men:
  - 4 non-comparative/non-prospective studies (n=104)
- Men and boys:
  - 1 non-comparative/non-prospective study (n=185)

Potent topical corticosteroids:
Direct evidence available for:

- Women:
  - 3 RCTs
    - Improvement of symptoms: GRADE ⊕⊕⊕⊕ high - ⊕◯◯◯ very low
    - Patient global assessment: GRADE ⊕⊕◯◯ low
    - Physician global assessment: GRADE ⊕◯◯◯ very low
  - 14 non-comparative/non-prospective studies (n=988)
- Girls
  - 1 non-comparative/non-prospective study (n=11)
- Boys
  - Cochrane review (1 RCT)
  - 2 non-comparative/non-prospective studies (n=83)

For specific results, see Evidence report

For each recommendation that is evidence-based, we added the certainty of the evidence (see also Figure 2).

High ⊕⊕⊕⊕: we are **very confident** that the true effect lies close to that of the estimate of the effect.
Medium ⊕⊕⊕◯: we are **moderately confident** in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕◯◯: our **confidence in the effect estimate is limited: The true effect may be substantially different** from the estimate of the effect.
Very low ⊕◯◯◯: we have **very little confidence** in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

FIGURE 2: DEFINITIONS OF "CERTAINTY OF EVIDENCE"[15]

Internal and external review

Internal review:

The guideline document, the methods report and the evidence report were send to all members of the guideline development group. All members of the guideline development group were required to review the documents. After the review phase (31.03.2023 – 17.04.2023) all comments were combined in an word documents by the EuroGuiDerm Team. Editorial comments were directly resolved by the EuroGuiDerm Team. All other comments were sent to the coordinator GK to be resolved. All changes to the guideline, the evidence report and the methods report were made using the "track changes" function. All reviewers received feedback to their comments alongside the GL and the evidence report

and methods report. An anonymised version of all comments, feedback and action taken are available from euroguiderm@debm.de.

External review:

The guideline document, the methods report and the evidence report as well as the review commenting form were send to: EDF Board and all supporting societies. After the review phase (06.06.2023 – 27.06.2023) all comments from the reviewer were combined in a word documents. Editorial comments were resolved by the EuroGuiDerm Team. All other comments were sent to the coordinator GK to be resolved. All changes to the guideline and the evidence report and the methods reports were made using the "track changes" function. All reviewers received feedback to their comments alongside the GL and the evidence report and the methods report. An anonymised version of all comments, feedback and action taken are available from euroguiderm@debm.de.

Dissemination and Implementation

We developed a dissemination and implementation plan, see Table 3.

Barriers and facilitators to implementation/application

Guideline implementation refers to the integration of the guideline recommendations into clinical practice, which can be influenced by various location- and setting-specific factors. A major challenge to implementation may be the discrepancies between national/local definitions of disease and treatment goals. Moreover, patients with lichen sclerosus are often managed by different specialists, each with their own approach, further complicating the implementation of a uniform guideline-based care approach.

We included various national societies and experts from 17 countries to promote national and local adoption/adaptation of the guideline. The national societies were kept informed about the status of the guideline development and were invited to form national review committees early on to encourage adoption/adaptation.

Quality standards and monitoring indicators

Over the two years following the publication of the EuroGuiDerm GL on EDF website we will assess:

- Number of accesses and/or downloads from the EDF website
- Number of countries which adopted (translated the guideline as is, without change of content) by European countries, regions and non-European countries
- Number of countries which adapted the guideline (used parts of the guideline, or some recommendations) by European countries, regions and non-European countries

Patient-perspective

Five patient representatives were part of the GDG, and they played an active role in the development of the guideline. They participated in the pre-votings and consensus meetings, where they had one vote each. Patient representatives also contributed to the development of several chapters (as can be seen in table 6), ensuring that the guideline reflects the needs and perspectives of patients with lichen sclerosus

Strength and Limitations

The guideline development group comprises 34 experts from 17 countries, including representatives of various medical disciplines and 5 patient representatives. This diverse group brought a range of perspectives to the guideline development process, enhancing its relevance and applicability to different settings.

The strength of the body of evidence presented lies within the application of rigorous and systematic methods as recommended by Cochrane and the GRADE working group, which we describe in detail here.

Nevertheless, the body of evidence identified regarding the treatment of lichen sclerosus is heterogeneous and limited, with studies reporting different outcomes and using diverse measurement methods. As a result, direct comparisons between interventions can be challenging. Furthermore, some interventions lacked sufficient evidence to allow for evidence-based recommendations, and some recommendations were developed on a consensus basis, as indicated in the guideline. Despite these challenges, we strived to provide the best possible guidance for the management of lichen sclerosus based on the available evidence and expert consensus.

Update and Methods

The expert panel will decide if and when an update is necessary, at the latest five years from the date of publication of the guideline.

Acknowledgements

We thank the British Association of Dermatologists (BAD) for providing the data from their systematic review. They kindly allowed us to utilize and update this data, which formed the evidence base for this guideline.

TABLE 3: DISSEMINATION PLAN

Audience	Responsible Subcommittee member(s)	Communication and/or implementation tools to be used	Time at which they are to be developed, piloted or to take place	Is EuroGuiDerm support needed, and if yes what kind of support?
Dermatology, Urology, Gynaecology, General Medicine, Patients / Patient Organisations, Research	G Kirtschig M Kinberger	Slide set (power point)	After external review	Assistance with slide set
Dermatology, Urology, Gynaecology, General Medicine, Patients / Patient Organisations, Research	EuroGuiDerm	Website	After external review	EuroGuiDerm Team to organize the website, layout etc
Dermatology, Urology, Gynaecology, General Medicine, Research	G Kirtschig EuroGuiDerm	Journal publication	Submission at the same time as the external review	Assistance with submission process
Dermatology, Urology, Gynaecology, General Medicine, Patients / Patient Organisations, Research	EuroGuiDerm Team	Twitter, EuroGuiDerm newsletter	Once the website is running, each time the publication is early online	EuroGuiDerm Team

Appendices

Appendix 1: E-mail send to funding societies

Dear XXXX

We thank xxxx for the support of the EDF – EuroGuiDerm Guidelines Center. A broad base for the funding is crucial for the project's success. We would like to invite you - as one of the supporting societies - to suggest one member to join the guideline development group.

The **EuroGuiDerm Lichen sclerosus Guideline** is now being updated.

We are looking for an established expert to become a member of the guideline development group, who ***preferably has little or no conflicts of interests with the pharmaceutical industry***. We are looking for dermatologists with at least 10 years' experience as a consultant (or equivalent) and a special **interest in lichen sclerosus.**

The nominated experts will be involved in writing the background texts and vote on the final guideline recommendations. The systematic search and literature appraisal will be done by the EuroGuiDerm center.

The deadline for nominations is September 7th, 2021. Please send your suggestions lichen-sclerosus@debm.de.

With best regards

Alexander Nast

For more information on EuroGuiDerm, please visit our website: https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

Prof. Dr. med Alexander Nast
Consultant Dermatologist/Clinical lead
Director of EuroGuiDerm
Department of Dermatology, Venerology und Allergy
Charité - Universitätsmedizin Berlin
Charitéplatz 1
D - 10117 Berlin
Germany

Appendix 2: E-mail send to Patient organisations and UEMS Soceities

Dear XXXX,

I am pleased to inform you that the update of the S3 Lichen sclerosus guideline of the European Dermatology Forum has started.

The main objective of the guideline is to develop specific diagnostic and therapeutic recommendations for lichen sclerosus.

The guideline is coordinated by Dr Gudula Kirtschig, MD. The EuroGuiDerm Guidelines Center is responsible for the methodological coordination of the project.

The experiences and perspectives of your organisation are very important for this interdisciplinary project. I would therefore like to invite your organization to participate by nominating an established expert to join the guideline development group. Ideally, he or she should have ***few or no conflicts of interests with the pharmaceutical industry*** and should be a xxxx with at least 10 years of experience as a consultant physician (or equivalent) and a **special interest in lichen sclerosus.**

The nominated expert will be involved in discussing and voting on the final guideline recommendations as part of an online consensus conference. The conference will consist of 1-2 meetings of approx. 4 hours' duration each, usually in the evening. He or she will also be involved in contributing to the writing of some of the background texts to the recommendations. The systematic search and literature appraisal will be conducted by the EuroGuiDerm center.

Please send the name and contact details of the proposed expert **before 8 September 2021** to **lichen-sclerosus@debm.de**

If your organisation is not able to participate in the project, I would also be grateful for a short feedback.

I am looking forward to the cooperation and remain with kind regards,

Alexander Nast

For more information on EuroGuiDerm, please visit our website:
https://www.edf.one/de/home/Guidelines/EDF-EuroGuiDerm.html

Prof. Dr. med Alexander Nast
Consultant Dermatologist/Clinical lead
Director of EuroGuiDerm
Department of Dermatology, Venerology und Allergy
Charité - Universitätsmedizin Berlin
Charitéplatz 1
D - 10117 Berlin
Germany

Appendix 3: Scoping document of the EuroGuiDerm Lichen sclerosus guideline – created in August 2021

EuroGuiDerm Lichen sclerosus guideline

SCOPING DOCUMENT

1. Planned methodological approach (guideline or consensus statement)

- *EuroGuiDerm Guideline on Lichen sclerosus*

2. Broadly defined scope population/region/setting/interventions/comparisons/outcomes

- *Population: Patients (all ages, all genders) with lichen sclerosus of all severities and localisations.*
    - *Female patients with vulval disease*
    - *Male patients with genital disease*
    - *Patients with extragenital involvement*
    - *Age groups to stratify for: 1) children (0-12) 2) adolescents (13-17), 3) adults (18+)*
    - *Pregnant women with lichen sclerosus*
- *Region: Europe*
- *Setting: Dermatologists, gynaecologists, urologists, pediater, proctologists and general practitioners in clinical practice*
- *Interventions/treatment approaches :*
    - *Topical treatment*
        - *Emollients*
        - *Corticosteroids (*clobetasol propionate, mometason furoate)
        - *Calcineurin inhibitors (*tacrolimus, pimecrolimus, ciclosporin)
        - *Retinoids (tretinoin,* 13-cis retinoic acid, retinaldehyde*)*
        - Topical hormone preparations
    - Intralesional corticosteroids (triamcinolone)
    - *Platelet rich plasma*
    - *UV therapy (UVB, UVA, PUVA)*
    - *Photodynamic therapy (PDT): ALA, MAL*
    - *Laser (CO2, erbium YAG laser)*
    - *Cryotherapy*
    - Systemic immunosuppressive treatment
        - systemic glucocorticosteroids
        - ciclosporin
        - methotrexate
        - hydroxyurea
        - retinoids (etrinate, acitretin)
    - Surgical interventions
- Comparisons: Direct, placebo or no treatment

- *Outcomes: The UK Dermatology Clinical Trials Network are currently conducting extensive exercises to develop a core outcome set in lichen sclerosus.* It was deemed unnecessary to repeat this process for the guideline development.

  As there is not yes a core outcome set published, we have decided on the following main outcomes:

  - *Quality of Life*
  - *Improvement of symptoms*
  - *Restoration of sexual function*
  - *Abolition of risk of cancer*
  - *Restoration of urinary function*
  - *Minor adverse events*
  - *Serious adverse events*
  - *Physician global assessment*
  - *Patient global assessment*

3. *Existing evidence and clinical guidance*

This section provides a general overview of existing systematic review and guidelines.

Guidelines

We conducted a non-exhaustive search in the Guidelines International Network (G-I-N), National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network *(SIGN), ECRI Guidelines Trust,* Association of the Scientific Medical Societies *(AWMF) and PubMed databases for existing guidelines published during the last 5 years, see* appendix 1.

We identified 14 guidelines. Eleven of these were evidence-based, and considered for adaptation:

- "Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus" by the European Dermatology Forum[16]
- "2013 European guideline for the management of balanoposthitis" by the European Academy of Dermatology and Venereology[17]
- "2014 UK national guideline on the management of vulval conditions" by the British Association for sexual health and HIV[18]
- "2016 European guideline for the management of vulval conditions" by the European Academy of Dermatology and Venereology[19]
- "Canadian Urological Association guideline on male urethral stricture" by the Canadian Urological Association[20]
- „Diagnostic criteria, severity classification and guidelines oflichen sclerosus et atrophicus" by the Japanese Dermatological Association[21]
- "British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018" by the British Association of Dermatologists[1]
- „Male urethral stricture: AUA Guideline" by the American Urological Association[22]

- *"Diagnosis and Management of Vulvar Skin Disorder" by the American College of Obstericians and Gynecologists*[23]
- *"British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018" by the British Association of Dermatologists*[24]
- "Guidelines on Paediatric Urology" by the European Society for Paediatric Urology, European Association of Urology[25]

AGREE II evaluations (domain 3 only) of these guidelines are shown below. Based on our evaluations, we decided to use the "British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018" by the British Association of Dermatologists.

Systematic reviews

Due to the high AGREE II rating of the British lichen sclerosus guideline and the resulting intention to adapt this guideline, a search for systemic reviews was not conducted.

4. The purpose and objectives of guideline/ consensus statement

Background:

- *New evidence available for the treatment of lichen sclerosus*
- *Several guidelines for diagnosis and treatment of lichen sclerosus exist, but recommendations vary and evidence-based recommendations are needed*
- *Different prescribing practices between dermatologists, gynaecologists and urologists across Europe and lack of experience have been reported. There is a need for current guidance, diagnostic and treatment algorithms as well as follow-up recommendations.*
- *Lack of guidance on the interdisciplinary management of patients by dermatologists, urologists and gynaecologists*
- *Underdiagnosed and uncertainty about the right diagnostic and treatment measures*[26, 27].

Objectives and aims:

- *To update the existing European Lichen sclerosus guideline based on up-to-date evidence*
- *To generate recommendations and algorithms on diagnosis and treatment for patients with lichen sclerosus*

5. *Targeted users of guideline/consensus statement*

- Dermatologists, gynaecologists and urologists, pediater, proctologists and general practitioners across Europe.

6. *Connecting with relevant other organisations*

- Involvement of patients: patient representatives will be part of the guideline development group.

7. *Stakeholder recruitment*

- National societies contributing financially to the EDF guidelines fund will be contacted via email with a call for experts.
- EDF members will be invited to self-nominate via the EuroGuiDerm newsletter twice.
- The guideline coordinator and the members of the EuroGuiDerm Board of Directors will also be invited to suggest members.
- The UEMS sections on dermatology, urology, gynaecology, paediatrics and coloproctology will be invited to nominate experts via mail.

8. *Other key issues*

- Lichen sclerosus may be associated with a significant impact on QoL, and there is a need for effective and safe (long-term) treatments.
- Economic evaluations based on interventions in children and adults with Lichen sclerosus are scarce. Resource use and costs vary according to country and health care systems, making extrapolation from one setting to another difficult.
- Interventions for improving access to care, patient education and treatment adherence should be explored. Furthermore, patients' preferences need to be taken into account.

9. *Proposed key questions*

<u>Evidence-based questions:</u>

(1) What is the efficacy and safety of emollients for female and male patients with Lichen sclerosus in different age groups?

(2) What is the efficacy and safety of topical and intralesional corticosteroids for female and male patients with Lichen sclerosus in different age groups?

(3) What is the efficacy and safety of topical calcineurin inhibitors for female and male patients with Lichen sclerosus in different age groups?

(4) What is the efficacy and safety of topical retinoides for female and male patients with Lichen sclerosus in different age groups?

(5) What is the efficacy and safety of topical testosterone and other hormonal treatments for female and male patients with Lichen sclerosus in different age groups?

(6) What is the efficacy and safety of surgery interventions for female and male patients with Lichen sclerosus in different age groups?

(7) What is the efficacy and safety of cryotherapy for female and male patients with Lichen sclerosus in different age groups?

(8) What is the efficacy and safety of photodynamic therapy for female and male patients with Lichen sclerosus in different age groups?

(9) What is the efficacy and safety of phototherapy for female and male patients with Lichen sclerosus in different age groups?

(10) What is the efficacy and safety of laser interventions for female and male patients with Lichen sclerosus in different age groups?

(11) What is the efficacy and safety of systemic therapies for female and male patients with Lichen sclerosus in different age groups?

(12) What is the efficacy and safety of *platelet rich plasma* treatment for female and male Lichen sclerosus patients of different age groups?

(13) What is first line, second line and third line treatment for female and male Lichen sclerosus patients of different age groups (treatment algorithm)?

(14) How long should patients with Lichen sclerosus be treated?

(15) Is maintenance therapy useful? If yes, what is the best maintenance therapy?

(16) How should lichen sclerosus be treated during pregnancy?

(17) How can the development of intraepithelial neoplasia or squamous cell carcinoma be prevented?

<u>Consensus-based questions:</u>

(18) What is the best diagnostic algorithm for male and female Lichen sclerosus patients in the different age groups?

(19) Should routine diagnostic measures be performed in Lichen sclerosus patients?

(20) What are the main differential diagnoses and how can they be distinguished?

(21) What are the important provocation factors for Lichen sclerosus and how should patients avoid them?

(22) Which instruments should be used to assess and monitor disease control in Lichen sclerosus patients?

(23) When is a presentation in gynaecology or urology advisable?

(24) Are effective patient education programmes available?

SCOPING DOCUMENT - Appendix: Existing Lichen schlerosus guidelines

Search terms

Lichen sclerosus ti/ab OR balanitis xerotica obliterans ti/ab (in PubMed additionally with "guideline*" in title)

Search date
13 July 2021

Titel	Organisation(s)	Date	Country/Region	Sources	Comments
Evidence-based (S3) Guideline on (anogenital) Lichen sclerosus[16]	European Dermatology Forum	Feb, 2017	Europe	PubMed	evidence-based
2013 European guideline for the management of balanoposthitis [17]	European Academy of Dermatology and Venereology	Aug, 2014	Europe	NICE, PubMed	evidence-based
2014 UK national guideline on the management of vulval conditions[18]	British Association for sexual health and HIV	Aug, 2015	United Kingdom	NICE, PubMed	evidence-based
2016 European guideline for the management of vulval conditions[19]	European Academy of Dermatology and Venereology	Jun, 2017	Europe	NICE, PubMed	evidence-based
Canadian Urological Association guideline on male urethral stricture [20]	Canadian Urological Association	Oct, 2020	Canada	PubMed	evidence-based
NHG-Standaard Lichen sclerosus (M101) [28]	Nederlands Huisartsen Genootschap	Nov, 2012	Nederlands	G-I-N	Language: dutch
Diagnostic criteria, severity classification and guidelines of lichen sclerosus et atrophicus[21]	Japanese Dermatological Association	Aug, 2018	Japan	PubMed	evidence-based
British Association of Dermatologists guidelines for the management of lichen sclerosus, 2018[1]	British Association of Dermatologists	Apr, 2018	United Kingdom	PubMed, ECRI, NICE	evidence-based
Guidelines for the follow-up of women with vulvar	International Society for the Study of	May, 2008	international	Pubmed	Not evidence-based

lichen sclerosus in specialist clinics [29]	Vulvovaginal Disease World Congress				
Male urethral stricture: AUA Guideline[22]	American Urological Association	Apr, 2016	America	ECRI, NICE	evidence-based
Diagnosis and Management of Vulvar Skin Disorder[23]	American College of Obstericians and Gynecologists	Jul, 2020	America	ECRI	evidence-based
British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018[24]	British Association of Dermatologists	Apr, 2019	United Kingdom	ECRI, NICE	evidence-based
Guidelines on Paediatric Urology[25]	European Society for Paediatric Urology, European Association of Urology	Mar, 2015	European	NICE	evidence-based
Commissioning guide: Foreskin conditions	British Associations of Urological Surgeons/ British Associations of Paediatric Surgeons/ British Associations of Paediatric Urologists	Jul, 2016	United Kingdom	NICE	Not evidence-based

Guidelines	7. Systematic methods were used to search for evidence.	8. The criteria for selecting the evidence are clearly described.	9. The strengths and limitations of the body of evidence are clearly described.	10. The methods for formulating the recommendations are clearly described.	11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	12. There is an explicit link between the recommendations and the supporting evidence.	13. The guideline has been externally reviewed by experts prior to its publication.	14. A procedure for updating the guideline is provided.	Quality score (0%-100%)
Guideline on Lichen sclerosus **Kirtschig et al. 2015**	Search in Databases: MEDLINE, MEDLINE process, Embase, Cochrane library; search date available; search strategy available; comprehensive search strategy	No clear inclusion and exclusion criteria described	Designs of studies used as evaluation of certainty of evidence; no RoB evaluation available	strength of recommendation depends on study design. No further information given on how consesus was reached or on voting results	Not all recommendations take safe aspects into account; weighing of benefits and risks in the background text	Each recommendation is presented in a box with level of evidence and evidence is decribed in the text; reference list for each section available	No information	Expiry date is mentioned but no further information	
Rating	7	2	2	2	5	7	1	5	48%
2013 European guideline for the management of balanoposthitis **Edwarts et al. 2014**	Search in Databases: Medline/ Pubmed, Embase, Cochrane Library up to June 2012; Guideline search in Google and from BAS HH and BAD up to June 2012; update search in Cochrane Database up to December 2012; search terms included 'balanitis,' 'balanoposthitis' and specific aetiologies but no specific search strategy was provided; imprecise search; exact date of search is not known; not enough information to replicate literature searches	No information	hardly any information; designs of studies used as evaluation of certainty of evidence; no RoB evaluation available	Strength of recommendation depends on study design; however, only very few studies are mentioned; no further information given on how consesus was reached	No assessment possible, as neither benefits nor safety aspects are sufficiently described.	Each recommendation is presented in a box with level of evidence; however, the evidence is hardly described; only very few studies are mentioned	No information	No information	
Rating	3	1	2	2	1	2	1	1	10%

2014 UK national guideline on the management of vulval conditions **Edwads et al. 2015**	Search in databases: Medline, Embase, Cochrane database up to March 2012; search terms were provided; imprecise search; screen of British Association of Dermatology and Green-top Guidelines	No information	hardly any information; designs of studies used as evaluation of certainty of evidence; no RoB evaluation available	Strength of recommendation depends on study design; however, only very few studies are mentioned; no further information given on how consensus was reached	No assessment possible, as neither benefits nor safety aspects are sufficiently described.	Each recommendation is presented in a box with level of evidence; however, the evidence is hardly described; only very few studies are mentioned.	The guidelines have been reviewed and approved by an expert patient, and by the British Association Sexual Health and HIV (BASHH); no information on how the external evaluation took place, what comments were made and how were dealt with; no information whether there was a methodological evaluation	Proposed review date was February 2018; no further information on process and project	
Rating	4	1	2	2	1	2	3	2	19%
2016 European guideline for the management of vulval conditions **van der Meijden et al. 2017**	Search in databases: MEDLINE, MEDLINE process, Embase, Cochrane library; search up to March 2015; search terms were provided; imprecise search; sexually transmitted diseases guidelines produced by the British Association for Sexual health and HIV were also screened	No information	Designs of studies used as evaluation of certainty of evidence; no RoB evaluation available	Strength of recommendation depends on study design; no further information given on how consensus was reached	Only for some recommendations, the safety aspects are explained in the background text; a consideration does not take place	Each recommendation is presented in a box with level of evidence; however, the evidence is hardly described.	No information	No information	
Rating	4	1	2	2	2	2	1	1	15%

Canadian Urological Association guideline on male urethral stricture **Rourke at al. 2020**	Update of the search by Wessels et al (AUA Guideline) in Medline, Embase and Cochrane database from, 1 January 2014 to 9 October 2018; search terms provided; search strategy provided; comprehensive search strategy; no specific search for Lichen sclerosus	Inclusion criteria according to a PICO available; exclusion criteria of study designs available; studies were excluded if more than 20% of the population had lichen sclerosus ; no extra criteria for the lichen sclerosus part	strength and limitation of the included studies were described; but not specific for lichen sclerosus	guideline panel developed the recommendations by consensus during two teleconference meetings. The strength of each recommendation was rated as either strong or conditional. Strong recommendations were made when all the desirable consequences of treatment out weighed the undesirable consequences . Conditional recommendations were made when the desirable consequences probably outweighed the undesirable consequences ; however no specific reommendation for lichen sclerosus	panel considered the desirable and undesirable effects of the interventions, the value placed on the outcomes, the required resources, the acceptability, the impact on health equity, and the feasibility of the interventions; benefits and side effects were reflected in the recommendations; however no specific recommendation for lichen sclerosus	recommendations directly linked to the evidence in the appendix; however no specific recommendation on lichen sclerosus	The final recommendations were reviewed and approved by the guideline panel. No information on external review	No information	
Rating	5	2	2	2	2	2	1	1	19%
British Association of Dermatologists guidelines for the management of lichen sclerosus **Lewis et al. 2018**	search terms, search strategies for Medline, Embase and Cochrane database available; search date available, top-up searches took place; reference screen for relevant citations in reviewed literature	Inclusion criteria according to a PICO available; reasons of study exclusion from quantitative analysis available	Evidence from included studies was graded according to the GRADE system; summary of evidence tables available; overall RoB assessment available	Recommendations were drafted based on the GDG's interpretation of the available evidence; The consensus recommendations were agreed through discussions in the GDG; no information on methods (conference, Delphi ...); no vote results for the recommendation available	efficacy and safety analysis available; both were reflected; sections on the balance between desirable and undesirable effects for interventions depending on population characteristics in the Appendix	summary of evidence for each treatment and each recommendation available	The draft document was made available for a 1-month consultation to all relevant stakeholders identified by the GDG, including healthcare professionals and patient support groups. All comments were reviewed by the GDG and the recommendations were revised if appropriate. Following further review, the finalized version was peer-reviewed by the Clinical Standards Unit of the BAD prior to submission to the British Journal of Dermatology.	The proposed revision date for this set of recommendations is scheduled for 2023; where necessary, important interim changes will be updated on the BAD website; no further information of update process	
Rating	7	7	6	5	7	7	7	5	90%

Male urethral stricture: AUA Guideline **Wessells et al. 2017**	Search in databases: Pubmed, Embase and Cochrane for time between 1 Jan 1990 and 12 Jan 2015; no search terms available, no search strategy available, no information whether there was a specific lichen sclerosus search	exact description of exclusion criteria; no PICO for inclusion criteria; no information on Lichen sclerosus specific search	Each recommendation is noted with a letter indicating the certainty of evidence; no further dealing of strength or limitation	letter of the recommendation correlates with certainty of evidence; when no evidence was available consensus statements were made using a modified Delphi technique; no information on voting results	systematic wording that reflects the benefit-harm ratio; but only two recommendations on lichen sclerosus. No coverage of the complete topic	description of the evidence after each recommendation; no direct certainty of evidence description; only two recommendations on lichen sclerosus. No coverage of the complete topic	The draft guidelines document was distributed to 90 peer reviewers. The panel reviewed and discussed all submitted comments and revised the draft as needed. Guideline was submitted for approval to the PGC and the AUA Science and Quality Councilr	Guideline is valided until 31 May 2021; no further information	
Rating	2	3	2	5	3	3	6	5	44%
Diagnostic criteria, severity classification and guidelines of lichen sclerosus et atrophicus **Hasegawa et al. 2018**	no information	no information	Each recommendation is noted with a letter indicating the certainty of evidence; no further dealing of strength or limitation, no RoB	it is only noted that the letter of the recommendation correlates with certainty of evidence. no further information is given on how the recommendation texts were created or whether there were any votes	weighing of benefits and risks in the background text behind each recommendation.	Each recommendation is presented with a letter which stands for the level of evidence. Evidence is described in the background texts behind each recommendation; it is not clear whether all available evidence is always addressed	No information	No information	
Rating	1	1	2	2	5	5	1	1	21%
Diagnosis and Management of Vulvar Skin Disorder **ACOG 20202**	Search in databases: MEDLINE and Cochrane Library; screening of documents of the American College of Obstetricians and Gynecologists; search for articles published between January 2000–February 2020; no search terms or search strategy available; search cannot be repeated, it is not clear whether a separate search strategy was used for lichen sclerosus	The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document;	Each recommendation is noted with a letter indicating the certainty of evidence; no further dealing of strength or limitation, no RoB	it is only noted that the letter of the recommendation correlates with certainty of evidence. no further information is given on how the recommendation texts were created or whether there were any votes.	there is sometimes but not always a little weighting in the background texts; only a few information is provided.	Each recommendation is presented with a letter which stands for the level of evidence. Little evidence is described in the background texts. Not for all recommendations evidence is described	No information	No information	

		no PICO available							
Rating	3	3	2	2	2	2	1	1	17%
Guidelines on Paediatric Urology **Radmayr et al. 2021**	Search in databases: Pubmed, Ovid, EMBASE and the Cochrane Central Register of Controlled Trials and the Cochrane Database for Systematic Reviews; some search strategies available but not for lichen sclerosus or phimosis (lichen sclerosus is part of the phimosis section)	search for systematic reviews; no further information; no PICO available	no specific part for Lichen sclerosus	no specific part for Lichen sclerosus	no specific part for Lichen sclerosus	no specific part for Lichen sclerosus	the old version of 2015 was peer-reviewed prior to publication	updated every year	
Rating	2	2	1	1	1	1	2	6	17%
British Association of Dermatologists and British Photodermatology Group guidelines for topical photodynamic therapy 2018 **Wong et al. 2019**	A systematic literature search of the PubMed, MEDLINE, Embase, Cochrane and AMED databases; search terms available; search startgy available; additional reference screening; no specific lichen sclerosus search	PICO available; not specific for lichen sclerosus (part of infectious and inflammatory dermatoses)	no recommendation on lichen sclerosus (because of insufficient evidence); available lichen sclerosus evidence is not described in guideline document	no lichen sclerosus recommendation	no lichen sclerosus recommendation	no lichen sclerosus recommendation	reviewing by BAD, BPG, BDNG, PCDS, Gorlin Syndrome Group, Clinical Standards Unit of the BAD; but no specific lichen sclerosus recommendation available for reviewing	proposed revision date is noted	
Rating	2	2	2	1	1	1	2	5	17%

Appendix 4: Search Strategies

PubMed carried out on 09.09.2021

#46 Search: **#36 OR #44** Filters: **from 2017/7/17 - 2021/9/9**
#45 Search: **#36 OR #44**
#44 Search: **#35 AND #43**
#43 Search: **#37 OR #38 OR #39 OR #40 OR #41 OR #42**
#42 Search: **immunosuppress*[Title/Abstract]**
#41 Search: **intervention*[Title/Abstract]**
#40 Search: **management[Title/Abstract]**
#39 Search: **treatment[Title/Abstract]**
#38 Search: **therapies[Title/Abstract]**
#37 Search: **therapy[Title/Abstract]**
#36 Search: **#16 AND #35**
#35 Search: **#21 OR #34**
#34 Search: **#22 OR #23 OR #27 OR #28 OR #33**
#33 Search: **#31 AND #32**
#32 Search: **#19 OR #20**
#20 Search: **lichen sclerosis[Title/Abstract]**
#19 Search: **lichen sclerosus[Title/Abstract]**
#31 Search: **#29 OR #30**
#30 Search: **penile[Title/Abstract]**
#29 Search: **penis[Title/Abstract]**
#28 Search: **#25 AND #26**
#27 Search: **#24 AND #26**
#26 Search: **xerotica[Title/Abstract]**
#25 Search: **balanitis[Title/Abstract]**
#24 Search: **balanitis[MeSH Terms]**
#23 Search: **xerotica obliterans[Title/Abstract]**
#22 Search: **balanitis xerotica obliterans[MeSH Terms]**
#21 Search: **#17 OR #18 OR #19 OR #20**
#18 Search: **vulvar lichen sclerosus[MeSH Terms]**
#17 Search: **lichen sclerosus et atrophicus[MeSH Terms]**
#16 Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15**
#15 Search: **cohort stud[Title/Abstract]**
#14 Search: **open stud*[Title/Abstract]**
#13 Search: **case control*[Title/Abstract]**
#12 Search: **case report*[Title/Abstract]**
#11 Search: **case series[Title/Abstract]**
#10 Search: **clinical monitor*[Title/Abstract]**
#9 Search: **controlled clinical trial*[Title/Abstract]**
#8 Search: **non-randomi* control trial*[Title/Abstract]**
#7 Search: **non-randomi* controlled trial*[Title/Abstract]**
#6 Search: **RCT*[Title/Abstract]**
#5 Search: **randomi* control trial*[Title/Abstract]**
#4 Search: **randomi* controlled trial*[Title/Abstract]**
#3 Search: **Randomized Controlled Trial[MeSH Terms]**
#2 Search: **systematic review[Title/Abstract]**

#1 Search: **meta-analys*[Title/Abstract]**

Ovid MEDLINE carried out on 09.09.2021

1	(meta-analys$2 or (systematic adj review$1) or (randomi$3 adj control$3 adj trial$1) or RCT$1 or (non-randomi$3 control$3 adj trial$1) or (control$3 adj clinical adj trial$1) or (clinical adj monitor$3) or (case adj series) or (case adj report$1) or (case adj control$1) or (open adj stud$3) or (cohort adj stud$3)).ab,kw,ti.
2	*Lichen Sclerosus et Atrophicus/ or *Vulvar Lichen Sclerosus/ or (lichen adj sclerosus).ab,kw,ti. or (lichen adj sclerosis).ab,kw,ti.
3	*Balanitis Xerotica Obliterans/ or ((*Balanitis/ or balanitis.ab,kw,ti.) and xerotica.ab,kw,ti.) or (balanitis adj xerotica).ab,kw,ti. or (xerotica adj obliterans).ab,kw,ti. or ((penis or penile) and ((lichen adj sclerosus) or (lichen adj sclerosis))).ab,kw,ti.
4	2 or 3
5	1 and 4
6	(therap$3 or treatment or management or intervention$1 or immunosuppress$3).ab,kw,ti.
7	4 and 6
8	5 or 7
9	("2017*" or "2018*" or "2019*" or "2020*" or "2021*").dt.
10	8 and 9

Embase Classic+Embase carried out on 09.09.2021

1	(meta-analys$2 or (systematic adj review$1) or (randomi$3 adj control$3 adj trial$1) or RCT$1 or (non-randomi$3 control$3 adj trial$1) or (control$3 adj clinical adj trial$1) or (clinical adj monitor$3) or (case adj series) or (case adj report$1) or (case adj control$1) or (open adj stud$3) or (cohort adj stud$3)).ab,kw,ti.
2	*Lichen Sclerosus et Atrophicus/ or *Vulvar Lichen Sclerosus/ or (lichen adj sclerosus).ab,kw,ti. or (lichen adj sclerosis).ab,kw,ti.
3	*Balanitis Xerotica Obliterans/ or ((*Balanitis/ or balanitis.ab,kw,ti.) and xerotica.ab,kw,ti.) or (balanitis adj xerotica).ab,kw,ti. or (xerotica adj obliterans).ab,kw,ti. or ((penis or penile) and ((lichen adj sclerosus) or (lichen adj sclerosis))).ab,kw,ti.
4	2 or 3
5	1 and 4 396
6	(therap$3 or treatment or management or intervention$1 or immunosuppress$3).ab,kw,ti.
7	4 and 6
8	5 or 7
9	("2017*" or "2018*" or "2019*" or "2020*" or "2021*").dc.
10	8 and 9 8

Cochrane carried out on 09.09.2021

1 lichen sclerosus

2 lichen sclerosis

3 MeSH descriptor [Lichen Sclerosus et Atrophicus] axplode all trees

4 MeSH descriptor [Vulvar Lichen Sclerosus] explode all trees

5 #1 or #2 or #3 or #4

6 Xerotica obliterans

7 MeSH descriptor [Balanitis Xerotica Obliterans] explode all trees

8 MeSH descriptor [Balanitis] explode all trees

9 Balanitis

10 Xerotica

11 (#8 or #9) and #10

12 #6 or #7 or #11

13 #5 or #12 with Cochrane Library publication date from Jul 2017 to Sep 2021

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