



Published in final edited form as:

*J Invest Dermatol.* 2015 January ; 135(1): 7–12. doi:10.1038/jid.2014.316.

## From pathogenesis, epidemiology, and genetics to definitions, diagnosis, and treatments of cutaneous lupus erythematosus and dermatomyositis: A report from the 3<sup>rd</sup> International Conference on Cutaneous Lupus Erythematosus (ICCLE) 2013

Heather Yarnall Schultz<sup>1</sup>, Jan P. Dutz<sup>2</sup>, Fukumi Furukawa<sup>3</sup>, Mark Goodfield<sup>4</sup>, Annegret Kuhn<sup>5</sup>, Lela A. Lee<sup>6</sup>, Filippa Nyberg<sup>7</sup>, Jacek C. Szepietowski<sup>8</sup>, Richard Sontheimer<sup>9</sup>, and Victoria P. Werth<sup>10,11</sup>

<sup>1</sup>Medical Writer, Huntington, West Virginia, USA <sup>2</sup>Department of Dermatology and Skin Science, University of British Columbia, Vancouver, CA <sup>3</sup>Department of Dermatology, Wakayama Medical University, Wakayama, Japan <sup>4</sup>Department of Dermatology, Leeds General Infirmary, UK <sup>5</sup>Department of Dermatology, University of Munster, Germany <sup>6</sup>University of Colorado, Denver, CO, USA <sup>7</sup>Karolinska Institutet at Danderyd Hospital, Stockholm, Sweden <sup>8</sup>Department of Dermatology, Venereology and Allergology, Medical University, Wroclaw, Poland <sup>9</sup>University of Utah, Salt Lake City, UT, USA <sup>10</sup>Philadelphia V.A. Medical Center, Philadelphia, PA, USA <sup>11</sup>University of Pennsylvania School of Medicine, Philadelphia, PA, USA

### Mission to Develop International Standards

The 3<sup>rd</sup> International Conference on Cutaneous Lupus Erythematosus (CLE) was held from May 6–8 in Edinburgh, Scotland in conjunction with the International Investigative Dermatology (IID) meeting. Approximately 50 researchers and clinicians representing North America, Europe, Asia, and Africa were in attendance. Building on previous meetings in Dusseldorf, Germany in 2004 and Kyoto, Japan in 2008, this third conference was organized by Drs. Jan Dutz, Fukumi Furukawa, Mark Goodfield, Annegret Kuhn, Lela Lee, Filippa Nyberg, Jacek Szepietowski, and Richard Sontheimer and overall meeting organizer Victoria P. Werth. The overarching goals of this conference were to provide an international forum for CLE researchers and clinicians to explore recent developments in basic science and translational and clinical studies; to develop approaches to allow the CLE community to reach consensus for uniform definitions, diagnostic criteria, and classification of CLE and systemic lupus erythematosus (SLE)-associated skin lesions; and to develop mechanisms for ongoing international collaborations. Furthermore, this meeting included discussions about the related autoimmune disease dermatomyositis (DM).

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Corresponding Author: Victoria P. Werth, Department of Dermatology, Perelman Center for Advanced Medicine Suite 1-330A, 3400 Civic Center Boulevard, Philadelphia, PA 19104, Tel. 215-823-4208, Fax 866-755-0625, werth@mail.med.upenn.edu.

Conflict of Interest

Biogen, Celgene, Genzyme, Pfizer, Rigel, and Stiefel provided support for this meeting.

Standard definitions and consensus classification are paramount in this field due to the current lack of standard definitions and categorization. Development of a standardized classification is critical to allow for collaboration across continents, interpretation of published studies, and conduction of clinical trials. To initiate the beginnings of a group effort to develop a classification scheme, several speakers presented background information related to the development of such a consensus. Dr. Joseph Merola (Harvard Medical School, Boston, MA) spoke about the Delphi technique (Dalkey and Helmer, 1963; Hsu and Sandford, 2007). This process involves a series of questionnaires delivered in multiple iterations to collect data from a panel of selected experts in the field of CLE. This technique has been used successfully in the past in related fields to develop classification criteria for systemic sclerosis, to define outcome domains for psoriasis, and to establish core domains to assess flare in rheumatoid arthritis (Bartlett *et al.*, 2013). One benefit of this technique is that diverse members of the scientific community have an equal voice in determining the final outcome.

Drs. Kari Connolly (University of California San Francisco), Jorg Wenzel (University of Bonn), Ben Chong (University of Texas Southwestern Medical Center, Dallas, TX), Melissa Costner (University of Texas Southwestern Medical Center), Annegret Kuhn (University of Munster), Asad Zoma (Glasgow University, Scotland), Lela Lee (University of Colorado), Richard Sontheimer (University of Utah), and Ingrid Lundberg (Karolinska Institute, Stockholm, Sweden) gave very informative presentations that outlined the current thinking about categorization of lesions and described current and historical classification criteria for cutaneous lupus erythematosus (LE), systemic LE, and dermatomyositis. In addition, the attendees split into three groups to discuss ideas regarding definitions, diagnosis, and classification. The groups presented summaries of their unique discussions to the whole group, prompting ample discourse among the group members. From here, the conference organizers plan to draw from the results of the subgroups to establish Delphi questionnaires, which will be filled out by the attendees as well as additional experts in the field. This meeting, therefore, was a first step toward acceptance of a universal standard for definition and classification system for CLE.

## Current Climate of CLE

### Pathogenesis

With more than 20 oral presentations and 11 posters (many of which are summarized here), the current state of research, epidemiology, and treatment of CLE was described by well-known experts in the field. As the role of environmental factors in the induction of autoimmune diseases remains unclear, the utilization of animal models of diseases offers a chance to examine these effects in detail. Repeated UV light exposure in NOD mice results in the induction of ANA in these animals (O'Brien *et al.*, 2006). Repeated topical imiquimod treatment may also induce an SLE phenotype in non-autoimmune prone animals (Yokogawa *et al.*, 2014). Dr. Jan Dutz presented data showing that treatment of non-obese diabetic (NOD) mice with repeated UV light exposure in combination with Toll-like receptor-7 (TLR7) engagement with imiquimod resulted in SLE-like disease with enhanced anti-nuclear antibody (ANA) and anti-Dsg3 antibody production, glomerulosclerosis, and serum

interferon (IFN)- $\alpha$  levels. The results obtained in this animal model are in agreement with the observed high levels of skin-specific autoantibodies in a subset of pediatric SLE patients (Li *et al.*, 2011). In addition, treatment of the mice with chloroquine prevented UV-induced ANA autoantibody production, supporting use of this drug as a treatment strategy. Dr. Min Ae Lee-Kirsch (Technical University Dresden, Germany) discussed the pathogenesis of TREX1-associated forms of CLE. A loss-of-function mutation in the TREX1, a DNA exonuclease with specificity for single-stranded DNA, was identified in chilblain lupus. TREX1 mutations have been identified in SLE patients in the UK and Germany. Mice homozygous for this mutation mount an autoimmune response and die; although, interbreeding with mice deficient for the IFN regulatory factor 3 permits survival of these mice. This result implicates IFN in the phenotype, consistent with IFN activation in TREX1-associated chilblain lupus patients. TREX1 variants confer a high risk of SLE, perhaps due to accrual of intracellular nucleic acid species and subsequent activation of the innate immune system via type 1 IFN.

Dr. Regine Gläser (University of Kiel, Germany) described the role of antimicrobial peptides (AMPs) in CLE. Because skin infections are rarely observed in CLE patients or psoriasis patients and psoriasis lesions contain high levels of AMPs, it is not surprising, then, that AMPs, including  $\beta$ -defensins 2 and 3, cathelicidin LL-37, and psoriasin are significantly induced in CLE skin compared to skin of healthy controls (Kreuter *et al.*, 2011). On the other hand, these AMPs serve as immune system alarmins and thus, may not be ideal in an autoimmune environment and may even be pathogenic (Harder *et al.*, 2013).

## Epidemiology

Dr. Mark Davis (Mayo Clinic, Rochester, MN) reported the results of a population-based study of 156 CLE patients from 1965–2005 from the Rochester Epidemiology Project (REP) database of patient records from Olmsted County, MN. Incidences of 4.30 cases of CLE, 3.56 cases of classic DLE, 0.63 cases of subacute CLE (SCLE), and 0.07 cases of lupus erythematosus panniculitis per 100,000 person years were calculated (Durosaro *et al.*, 2009). These values were similar to previous published incidences of SLE and thus, CLE is nearly as common as SLE. Approximately 12% of CLE cases progressed to SLE. Dr. Fukumi Furukawa described the results of genome-wide association studies to determine the epidemiology of the subtypes of CLE in Asia and highlighted the differences between Asian and Caucasian populations. SCLE is rare in Asia, likely due to the lack of the genetic HLA-DR3 allele in the population; however, this subtype occurs more commonly in 24% of CLE cases in Caucasians in the United States and Europe. In contrast, Sjogren's syndrome annular erythema is more common in Japanese compared to Caucasian populations. Dr. Filippa Nyberg presented the results of a population-based cohort study of CLE patients in 1088 individuals in Sweden (Gronhagen *et al.*, 2011). The incidence of CLE was found to be 4 per 100,000. Approximately 80% of cases were DLE, 15.7% were SCLE, and 4.5% were other subtypes. More than 10% of DLE cases progressed to SLE within a year, and more than 20% of SCLE patients progressed to SLE within 1 year. In another study of drug-induced SCLE, more than 38% of cases were found to be associated with exposure to drugs within 6 months of diagnosis; although, the absolute risk of developing SCLE from a medication is small (Gronhagen *et al.*, 2012). Dr. Annegret Kuhn presented the suggested

“Duesseldorf Classification”, which was published in the context of the first ICCLE 2004 in Duesseldorf, Germany, including LET as the intermittent subtype of CLE (ICLE) (Kuhn and Lehmann, 2004). In addition, Dr. Annegret Kuhn delivered an update on the European Society of Cutaneous Lupus Erythematosus (EUSCLE) and the core set questionnaire, which was originally published in 2009 with the aim to contribute to standardized assessment and monitoring of CLE and to develop diagnostic and therapeutic guidelines (Kuhn *et al.*, 2009). Since then, 1002 patients from 30 centers in 14 countries were included in the database, documenting the clinical subtypes of this disease (ACLE 30.3%, SCLE 23.6%, CCLE 39.6%, and ICLE 6.5%) (Biazar *et al.*, 2013). Recently, a consecutive study evaluated the preventive and therapeutic strategies used for these patients (Sigges *et al.*, 2013). Sunscreens were applied by 84.0% of the study cohort and showed an overall efficacy of 94.7% in the prevention of skin lesions.

Topical steroids were used in 81.5% of the CLE patients, with an efficacy of 88.4%, whereas systemic drugs, such as antimalarials and several immunomodulating/suppressive drugs including systemic steroids and methotrexate, were applied in 84.4% of the 1002 patients.

### Treatment

Dr. Sue Jessop (University of Cape Town, South Africa) gave a thorough summary of current CLE treatment options and the quality of the available evidence for each option. While much of the evidence stems from case reports, uncontrolled studies, and short trials, physician experience in clinical practice adds perspective and has been important in determining treatment approaches (Jessop *et al.*, 2009).

Dr. Thomas Ruzicka (University of Dusseldorf, Germany) presented an overview of current topical treatment strategies for CLE. While corticosteroids are often the first-line treatment for CLE and are often very effective, case reports and a multicenter randomized controlled trial using tacrolimus 0.1% ointment have suggested that the calcineurin inhibitors may be a good alternative in patients that do not respond to corticosteroids or those where corticosteroids are contraindicated (Kuhn *et al.*, 2011). This drug has several advantages, including rapid onset, safety during long-term use, few side effects, and low risk of infections and lymphoma; however, tacrolimus ointment is more expensive, has lower overall efficacy compared to corticosteroids, and may induce troublesome local side effects.

Antimalarials have been used to treat symptoms of CLE and SLE for decades as these drugs modulate the immune system without predisposing patients to infection. Dr. Camille Frances (Hopital Tenon, Paris, France) chronicled the evidence for first-line systemic treatment of CLE with these agents. A study of 300 patients with CLE demonstrated that higher blood levels of hydroxychloroquine were associated with efficacy (Frances *et al.*, 2012). Unfortunately, hydroxychloroquine is associated with ocular toxicity (0.4%), and skin pigmentation is a troubling side effect of long-term use (Jallouli *et al.*, 2013). Changing the antimalarial drug used for treatment did not lead to relapse of disease in a report of several patients. Dr. Elisabeth Aberer (Medical University of Graz, Austria) described the use of dapsone and retinoids as second-line treatments for lupus for CLE. Dr. Aberer’s group performed a retrospective study of dapsone treatment of 34 patients with CLE previously treated unsuccessfully with chloroquine or hydroxychloroquine. Fifty-eight percent of these

patients exhibited healing or improvement of cutaneous lesions. All tested subtypes of CLE (DLE, SCLE, LET, and SLE) responded, and only four patients required discontinuation of medication due to adverse reactions. Retinoids, including etretinate, acitretin, and isotretinoin, have exhibited good efficacy in the treatment of DLE, SCLE, CLE, and SLE patients in case series and small studies. Dr. Werth noted an 80–90% overall response rate to thalidomide in SCLE and DLE; however, a high relapse rate (up to 70%) and a high incidence of neurotoxicity has spurred additional investigation into potentially less neurotoxic thalidomide analogs, such as lenalidomide. While abatacept has not demonstrated reliable efficacy in placebo-controlled trials, the anti-B lymphocyte stimulator antibody belimumab was shown to reduce SLE activity scores and was approved for use in refractory SLE cases. Additional work on the use of this drug for CLE is warranted.

Dr. Miriam Wittman (University of Leeds, United Kingdom) noted that a high percentage of patients with SCLE and DLE exhibited vitamin D deficiency or insufficiency. CLE patients were observed to have low vitamin D levels in both summer and winter, while healthy individuals exhibited an increase in summer months (Renne *et al.*, 2008). These findings are plausibly explained by photoprotection combined with inadequate vitamin D supplementation. Vitamin D provides a myriad of functions in cellular growth and immune function, and low levels of vitamin D were found in CLE patients with higher IFN levels, indicating higher disease activity. Thus, vitamin D supplementation may be beneficial for these patients. A recent study showed that SLE patients exhibited higher vitamin D levels, lower disease activity scores, and decreased anti-DNA antibody levels following vitamin D supplementation (Terrier *et al.*, 2012).

Dr. Goodfield presented work on the use of stem cell therapy to treat SLE. Stem cell transplantation, mainly hematopoietic stem cell transplantation, has been used successfully to treat SLE patients with life-threatening disease; although, no data specific to skin manifestations have been reported. This treatment regime carries high mortality risk but can be effective in disease control despite risks of relapse, secondary autoimmune disease, and malignancy. Indeed, one study of 28 SLE patients treated with stem cell transplantation indicated a 5-year-survival rate of 81% and a relapse incidence of 56%. More recently, use of multipotent mesenchymal stem cells from umbilical cord blood cells has been investigated as a means of transplant therapy as these cells have low immunogenic potential and can be delivered locally or systemically. Studies in 2010 and 2012 in patients with life-threatening SLE indicated great promise for this therapy as clinical remission (28% at 1 year and 50% at 4 years) was achieved in many patients with low relapse (0–23%) and no treatment-related mortality or severe adverse effects.

Dr. Simon Meggitt (Newcastle University, United Kingdom) presented data demonstrating that current smokers had a significantly higher risk of SLE/CLE and higher disease activity scores than either ex-smokers or those who never smoked, and current smokers also exhibited a higher frequency of anti-dsDNA autoantibodies than those in the other groups. Smoking has also been specifically associated with cutaneous manifestations in SLE. At least two recent studies have demonstrated that smoking does not have an effect on the response of CLE patients to antimalarials.

Treatment of CLE is based primarily on personal experience. Dr. Jacek Szepietowski described the results of a survey of dermatologists from 51 clinics in Japan, the United States, and Europe to ascertain the current practice variation in CLE therapy. Results of these surveys described extreme variation in treatment modalities, treatment of the different subtypes, use of topical versus systemic therapy, the length of time before modification of therapy, and parameters used to assess efficacy in CLE treatment. For example, 14% of the dermatologists reported that systemic treatment was offered to CLE patients immediately, while 18% offered this therapy after one topical treatment failure, 33% offered this therapy after two topical treatment failures, 14% offered this therapy after three topical treatment failures, and 4% never offered this treatment option. In addition, 33% of the dermatologists assess CLE activity at each visit, but 6% only assess disease activity every 6 months. These findings underscore the need for expert consensus on definitions and classification as well as the need for multicenter clinical trials using contemporary methodology in order to improve patient care standards globally.

## Describing the Details of Dermatomyositis

### Pathogenesis

Dr. Manabu Fujimoto (Kanazawa University, Japan) described autoantibody-based classification of DM based on Japanese studies. Approximately 75% of DM patients are positive for myositis-specific autoantibodies (MSAs), including antibodies to synthetase, Mi2, MDA5, and Transcriptional Intermediary Factor 1 (TIF1) in the muscle fibers. In addition, Nuclear Matrix Protein-2 (NXP-2) and SAE antibodies have been identified in some of the remaining patients. MSA profiles have been associated with distinct clinical subsets and appear to be useful in diagnosis and classification of DM. According to recent studies these autoantigens are ubiquitously expressed in everyone, but the expression of these antigens is upregulated in certain circumstances (Casciola-Rosen *et al.*, 2005; Mammen *et al.*, 2009; Tsai *et al.*, 2010; Yokoe *et al.*, 2010). For example, the Jo-1 antigen, HisRS, and Mi-2 are expressed at low levels in normal muscle but at high levels in myositis muscle or regenerated muscle. Additionally, it is noteworthy that TIF1 antigens, which are predominantly targeted in cancer-associated DM, are overexpressed in some cancer tissues. Thus, overexpressed autoantigens may have a role in amplifying autoimmune responses that target muscles and related tissues. Dr. David Fiorentino (Stanford University, Palo Alto, CA), most (83%) cancer-associated DM patients had antibodies to either NXP-2 or TIF1 $\gamma$ , and thus, the absence of these autoantibodies was strongly predictive of a lack of cancer in DM patients. More specifically, NXP2 autoantibodies predicted male patients with cancer (Fiorentino *et al.*, 2013). Importantly, an autoantibody profile for all of these antigens indicated the clinical phenotype for 85% of DM patients in the United States, suggesting the clinical relevance of such a profile.

Dr. Naoko Okiyama (Tokyo Medical and Dental University, Japan) described a murine model of autoimmune myositis induced by immunization with muscle-specific antigens. The skeletal C-protein-induced myositis (CIM) model, which is superior to common mouse models of this disease due to the ability to induce the disease in a B6 genetic background and the fact that the disease mimics muscle injury observed in polymyositis, suggest that

muscle-specific CD8 T cells mediate cytotoxicity that is responsible for muscle fiber injury in these animals. In these mice, development of autoimmune myositis requires not only autoreactive T cells but also activation of innate immunity in the muscle fibers. Translational research using the CIM model suggested that blockade of inflammatory cytokines such as interleukin (IL)-6, IL-1, or tumor necrosis factor (TNF)- $\alpha$ , may be effective treatments for autoimmune myositis (Sugihara *et al.*, 2007, Okiyama, 2009 #7480).

## Epidemiology

Dr. Mark Davis (Mayo Clinic) described a population-based study of the incidence of DM and clinically amyopathic DM (CADM). Using data from the REP for residents of Olmsted County, MN since 1966, estimates for the incidence of DM were 9.63 per million persons, with CADM accounting for 20% of cases (Bendewald *et al.*, 2010). Dr. Minoru Hasegawa (Kanazawa University, Japan) discussed the characteristics of cancer-associated DM. A high percentage of adult DM patients (72% of those over the age of 40% and 85% of those over the age of 60) with malignancy had autoantibodies that recognize TIF1, suggesting the possibility that these antibodies may be produced during misdirected antitumor responses. Dr. Chia-Chun Ang (University of Pennsylvania) described the current understanding of lung complications in DM, which occur in up to 46% of DM/PM patients (Morganroth *et al.*, 2010). While the presence of autoantibodies is associated with an increased risk of ILD, a significant number of myositis patients have ILD without detectable antibodies, suggesting that diagnosis and prognosis require additional parameters.

## Quality of Life

Dr. Saroj Verma (University of Pennsylvania) described the effects of CLE and DM on patient quality of life (QoL), which is a critical aspect to consider for clinical practice. As expected based on prior studies of SLE, CLE disease activity has a significant effect on QoL, although, disease-related damage does not have such a significant effect (Verma *et al.*, 2014). QoL as assessed by the Skindex-29 and the SF-36 tools was worse for both CLE and DM patients than for those with other skin diseases (Goreshi *et al.*, 2011). In addition, the mental health measures were lower for CLE and DM patients than for those with myocardial infarction, diabetes, and hypertension. Ethnic differences were observed in CLE patients, as African-American patients experienced damage earlier in conjunction with disease activity (Verma *et al.*, 2014). In addition, photosensitivity and pruritus contributed to the poor QoL observed in the CLE and DM patients.

## Treatment

Dr. Beatrix Volc-Platzer (Donauspital/SMZ Ost, Vienna, Austria) presented evidence for treatment options for DM. High-dose corticosteroids are the mainstay of treatment with up to 90% of patients responding favorably, despite the lack of controlled studies. Second-line immunosuppressants, including methotrexate, azathioprine, and mycophenolate mofetil, may also be effective in combination with corticosteroids, with methotrexate being better tolerated than azathioprine. Nevertheless, these steroid-sparing agents should be introduced as early as possible. Methotrexate, mycophenolate mofetil and chloroquine and hydroxychloroquine are successful in controlling skin disease - albeit after some time of treatment. The antimalarials may be used either as single agent or combination treatment. In

the absence of successful control of disease with these options, and in particular with regard to refractory muscle disease, IVIg may be used. Therapeutic efficacy has been demonstrated in a randomized, controlled crossover study (Dalakas et al, 1993). A more recent study to investigate the efficacy of IVIg in 19 patients with idiopathic or paraneoplastic DM demonstrated that patients could be categorized into two groups: non-responders with higher muscle enzyme activity, higher serum sIL-2R levels, and severe skin and muscle disease and responders with lower muscle enzymes that were reduced following treatment, lower sIL-2R levels that decreased following treatment, and severe skin but moderate muscle disease. Overall, the response rate to IVIg was 37% (Gottfried *et al.*, 2000). Recent promising work has suggested that subcutaneous Ig or low-dose IVIg may be an effective alternative. Several open label studies indicated that rituximab may be an effective treatment for myositis. In 2013 the largest controlled trial was performed in adults and children with dermatomyositis and polymyositis (Oddis *et al.*, 2013). Although the study did not meet its defined outcome parameters, results indicated that rituximab has a steroid-sparing effect and that children may benefit from rituximab.

## Conclusions

The success of this international meeting reflects global interest of the CLE community to develop collaborative efforts to understand this disease and to pursue more effective treatments. Efforts were started to pursue a Delphi technique-driven approach to consensus in definitions, diagnostic criteria, and classification. In the future, the group plans to host a satellite meeting at the next World Congress of Dermatology in Vancouver in order to continue advancement on these topics.

## Acknowledgments

We thank Sean Wood for great secretarial assistance and Advancing Innovation in Dermatology, Biogen, Celgene, Genzyme, Pfizer, Rigel, and Stiefel for supporting this meeting. Funds were used in part to support the work of HYS who summarized the meeting and wrote the initial draft of this communication.

Support was also provided by the Department of Veterans Affairs Veterans Health Administration, Office of Research and Development, Biomedical Laboratory Research and Development and by the National Institutes of Health (NIH K24-AR 02207) to VPW.

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