Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry

L. Guillevin¹, E. Hunsche², C.P. Denton³, T. Krieg⁴, B. Schwierin², D. Rosenberg²
M. Matucci-Cerinic⁵, for the DUO Registry Group

¹Department of Internal Medicine, Centre de Référence pour les Vascularites Nécrosantes et la Sclérodermie Systémique, Hôpital Cochin, Assistance Publique–Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, France; ²Actelion Pharmaceuticals Ltd., Allschwil, Switzerland; ³Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK; ⁴Department of Dermatology, University of Köln, Köln, Germany; ⁵Department of Rheumatology AUC, Department of Medicine, Donothe Centre, University of Florence, Florence, Italy.

Loïc Guillevin, MD
Elke Hunsche, PhD
Christopher P. Denton, PhD, FRCP
Thomas Krieg, MD
Barbara Schwierin, PhD
Daniel Rosenberg, PhD
Marco Matucci-Cerinic, MD

Please address correspondence to:
Loïc Guillevin, MD,
Hôpital Cochin,
27 rue du Faubourg Saint-Jacques,
75014 Paris, France.
E-mail: loic.guillevin@cch.aphp.fr

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Abstract

Objective. Digital ulcers (DUs) are frequent manifestations of systemic scleroderma (SSc). This study assessed functional limitations due to DUs among patients enrolled in the Digital Ulcer Outcome (DUO) Registry, an international, multicentre, observational registry of SSc patients with DU disease.

Methods. Patients completed at enrolment a DU-specific functional assessment questionnaire with a 1-month recall period, measuring impairment in work and daily activities, and hours of help needed from others. Physician-reported clinical parameters were used to describe the population. For patients who completed at least part of the questionnaire, descriptive analyses were performed for overall results, and stratified by number of DUs at enrolment.

Results. This study included 2327 patients who completed at least part of the questionnaire. For patients with 0, 1–2, and ≥3 DUs at enrolment, mean overall work impairment during the prior month among employed/self-employed patients was 28%, 42%, and 48%, respectively. Across all included patients, ability to perform daily activities was impaired on average by 35%, 54%, and 63%, respectively. Patients required a mean of 2.0, 8.7, and 8.8 hours of paid help and 17.0, 35.9, and 63.7 hours of unpaid help, respectively, due to DUs in the prior month. Patients with DUs had more complications and medication use than patients with no DUs.

Conclusion. With increasing number of DUs, SSc patients reported more impairment in work and daily activities and required more support from others.

Introduction

Systemic scleroderma (SSc) is a rare multisystem autoimmune disorder with an estimated prevalence of approximately 2 per 10,000 adults (1, 2). SSc is commonly classified into two major subtypes on the basis of clinical features: diffuse cutaneous SSc is characterised by rapidly progressive fibrosis of the skin and internal organs, whereas limited cutaneous SSc is typified by vascular manifestations, with limited skin and organ fibrosis (1). Digital ulcers (DUs) on the fingertips, finger creases, or extensor surfaces of joints are a frequent complication in both SSc subsets (3). DUs occur in 36%–58% of SSc patients over the disease course (3-5); they are a major factor of morbidity by leading to infection, gangrene, and need for amputation or sympathectomy (4, 6).

Although few studies have investigated the effect of SSc-related DUs on patient disability, available evidence shows that DUs contribute to limiting hand function and the ability to perform housekeeping tasks, work, and have a normal personal and professional life (7-11). Prior studies have assessed the association between DUs and work or daily activities in patients with DUs compared with patients with no DUs (7-9), or among patients with different degrees of DU disease severity (10, 11), but no studies were multi-country, of large sample size, nor distinguished between patients with no DUs, a few DUs and patients with many DUs on their hands.

In this analysis from the multinational, European DUO Registry, SSc patients are categorised in three groups of DU severity, as measured by number of DUs at enrolment: patients with no DU (0 DU), those with a few (1–2) DUs, and those with many (≥3) DUs at enrolment. In order to assess the association between number of DUs and patients’ ability to function in normal daily life, patients are described in terms of their self-reported ability to work, to perform daily activities and their need...
for paid and unpaid help – all related to the last month prior to enrolment. In addition, clinical characteristics at enrolment are reported.

Materials and methods

Design and patients
The Digital Ulcer Outcome (DUO) Registry is a multicentre, prospective, observational cohort study of patients in Europe with a history of DU associated with SSc. The DUO Registry, sponsored by Actelion Pharmaceuticals Ltd., is a post-approval commitment for bosentan to the European Medicines Agency (EMA) and was started in April 2008. Actelion and an independent Scientific Committee of SSc experts were responsible for designing the DUO Registry protocol, Case Report Form (CRF), and analysis plan. Data collection and statistical analyses were performed by Actelion. The Scientific Committee was included in the review of the data. Actelion and the Scientific Committee were jointly involved in the decision to publish these analyses.

Eligible patients are those presenting with SSc and a history of DU disease in the past and/or DUs at time of enrolment into the registry, regardless of treatment. The DUO Registry collects data on DU disease history, severity at enrolment, and disease course, irrespective of treatment regimen (Actelion trial ID: AC-052-514) (12). The DUO Registry protocol defines DU as a denuded area with defined border and loss of epithelialisation, loss of epidermis and dermis, excluding fissures, paronychia, extrusion of calcium, or ulcers over the metacarpophalangeal joints.

The goal of the present analysis from the DUO Registry was to describe the association between the number of DUs and work, daily activities, and help needed in patients with SSc. Patients who were enrolled up to 19 November 2011 and completed at least part of the functional assessment questionnaire at their enrolment visit were considered for this analysis. Patients were recruited from Austria, the Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK. The registry protocol, the patient informed consent form, and other relevant information were submitted to the health authorities, data protection agencies, and the relevant independent ethics committees, according to national requirements and in compliance with local laws (12). Ethical approval was granted by the institutional ethics committees of participating centres when applicable or required. At participating centres, all SSc patients with DU who had given written consent were enrolled.

Data collection
In the DUO Registry, patients undergo clinical assessments and receive standard medical care as determined by their physicians, with no protocol-driven visits or tests. All components of the CRF, including patients’ socio-demographic and clinical features as well as data from patient-completed functional assessment questionnaires, are recorded in a Web-based electronic data capture system.

At the enrolment visit, the following data are collected by the investigator: demographic characteristics (including patient age, gender, body weight, and height), SSc disease classification, dates of first Raynaud and non-Raynaud manifestations and DU, presence or absence and type (if present) of internal organ SSc manifestations, number of DUs, DU complications, and medications.

Functional assessment
At the enrolment visit, patients are asked to complete a functional assessment questionnaire that was specifically designed for the DUO Registry based on the existing, validated Work Productivity and Activity Impairment Questionnaire (WPAI) (13). The WPAI was adapted together with the Scientific Committee and amended (including questions on help needed) taking into account design features of the DUO Registry. The questionnaire was translated into the various languages used in the participating countries. Patients are not compensated for completing the questionnaire. The questionnaire solicits patient-reported evaluations of the extent to which problems associated with ulcers of the fingers (i.e. DU-associated problems) affected their ability to work and perform regular daily activities, and their need for help from others. Work impairment is determined based on employment status, work days or hours missed, normal working hours per week, and productivity impairment while working. Patients score their productivity impairment using a scale from 0 (DU-associated problems had no effect on work) to 10 (DU-associated problems completely prevented work). Impairment of daily activities other than work is also scored from 0 (DU-associated problems had no effect on daily activities) to 10 (DU-associated problems completely prevented doing daily activities). The need for help is quantified as days or hours of paid and unpaid help needed. For all functional assessment questions, the recall period is the month prior to enrolment. To analyse responses to the questions on productivity and daily activity impairment, scores on the scales from 0 to 10 were transformed to impairment percentages. Work time missed was expressed as the percentage of actual hours missed during the past month out of the expected number of hours normally worked during the past month. Overall work impairment (expressed as a percentage) was calculated as the sum of work time missed and lost productivity at work (i.e. work time attended multiplied by the work impairment percentage).

Statistical analysis
Data were summarised by counts and percentages, means and 95% confidence intervals. Patients were categorised according to number of DUs on fingers at the enrolment visit: either 0 DU, 1–2 DUs, or ≥3 DUs. To avoid the risk of spurious results among the large number of comparisons, p values were not calculated for between-category comparisons (14). In order to quantify the precision of estimated levels of impairment, 95% confidence intervals were calculated. Missing values were not imputed except if “work hours missed” was not reported but “productivity impairment
due to DU was reported, then “work hours missed” was imputed to be 0. If hours of paid or unpaid help were not reported but the question whether the patient needed help was answered, missing hours of either paid or unpaid help were imputed to be 0.

To exclude outlying values that could yield unrealistic results, the maximum possible number of monthly work hours and monthly work hours missed was fixed at 42 per week multiplied by 4.3, based on the longest legal working week in any European country in the DUO Registry. Analyses were performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

### Results

As of the data extraction taken on 19 November 2011, 3383 patients were enrolled in the DUO Registry. Of these, 2327 (69%) patients from 286 centres in 18 European countries completed at least one part of the functional assessment questionnaire at the time of enrolment and were included in this analysis set. Five countries accounted for more than 80% of patients: France, Germany, Italy, Spain, and the UK.

### Functional assessment

#### Association between number of DUs and work impairment

Of the 784 (34%) respondents who were employed/self-employed, 576 (73%) completed the work-related...
Table II. Complications on fingers associated with digital ulcers and medication use at enrolment.

<table>
<thead>
<tr>
<th>Complications, n/N (%)</th>
<th>0 DU (n=747)</th>
<th>1–2 DUs (n=981)</th>
<th>≥3 DUs (n=592)</th>
<th>All* (n=2327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one</td>
<td>46/740 (6)</td>
<td>316/796 (42)</td>
<td>211/592 (36)</td>
<td>574/2307 (25)</td>
</tr>
<tr>
<td>Critical digital ischemia†</td>
<td>27/488 (6)</td>
<td>145/619 (23)</td>
<td>116/338 (34)</td>
<td>289/1449 (20)</td>
</tr>
<tr>
<td>Gangrene</td>
<td>4/740 (1)</td>
<td>91/973 (9)</td>
<td>68/582 (12)</td>
<td>163/2299 (7)</td>
</tr>
<tr>
<td>Autoamputation</td>
<td>3/734 (0)</td>
<td>28/965 (3)</td>
<td>31/576 (5)</td>
<td>62/2279 (3)</td>
</tr>
<tr>
<td>Soft tissue infection requiring systemic antibiotics</td>
<td>16/740 (2)</td>
<td>157/968 (16)</td>
<td>99/580 (17)</td>
<td>272/2292 (12)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>3/737 (0)</td>
<td>12/971 (1)</td>
<td>15/582 (3)</td>
<td>30/2294 (1)</td>
</tr>
<tr>
<td>Medication use, n/N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analgesics and anti-inflammatories</td>
<td>347/474 (47)</td>
<td>567/981 (58)</td>
<td>366/592 (62)</td>
<td>1283/2327 (55)</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>248/474 (33)</td>
<td>292/981 (30)</td>
<td>213/592 (36)</td>
<td>754/2327 (32)</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td>33/474 (4)</td>
<td>207/981 (21)</td>
<td>133/592 (23)</td>
<td>374/2327 (16)</td>
</tr>
<tr>
<td>Endothelin receptor antagonists</td>
<td>344/474 (46)</td>
<td>452/981 (46)</td>
<td>326/592 (55)</td>
<td>1125/2327 (48)</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>297/474 (40)</td>
<td>471/981 (48)</td>
<td>277/592 (47)</td>
<td>1049/2327 (45)</td>
</tr>
<tr>
<td>Prostacyclines</td>
<td>235/474 (31)</td>
<td>457/981 (47)</td>
<td>277/592 (47)</td>
<td>968/2327 (42)</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors</td>
<td>45/747 (6)</td>
<td>53/981 (5)</td>
<td>31/592 (5)</td>
<td>129/2327 (6)</td>
</tr>
<tr>
<td>Topical DU treatments</td>
<td>54/747 (7)</td>
<td>325/981 (33)</td>
<td>195/592 (33)</td>
<td>577/2327 (25)</td>
</tr>
</tbody>
</table>

*Includes 7 patients with missing information on number of DUs; †Number of patients with data on complication; ‡Defined in the CRF as follows: “This is not a Raynaud’s phenomenon. It is a prolonged severe persistent reduction in digital tissue perfusion without re-warming”; DU, digital ulcer.

Table III. Work status and impairment due to digital ulcers in the prior month.

<table>
<thead>
<tr>
<th>Work status and impairment due to digital ulcers</th>
<th>0 DU (n=747)</th>
<th>1–2 DUs (n=981)</th>
<th>≥3 DUs (n=592)</th>
<th>All* (n=2327)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed/self-employed, n (%)</td>
<td>247 (33)</td>
<td>336 (34)</td>
<td>198 (33)</td>
<td>784 (34)</td>
</tr>
<tr>
<td>Patients completing work part of questionnaire, n’</td>
<td>195</td>
<td>239</td>
<td>140</td>
<td>576</td>
</tr>
<tr>
<td>Normal working hours per week, mean (95% CI)</td>
<td>32.1 (30.7, 33.4)</td>
<td>30.2 (28.9, 31.5)</td>
<td>30.9 (29.2, 32.6)</td>
<td>31.0 (30.2, 31.8)</td>
</tr>
<tr>
<td>Work hours missed due to DUs, prior month, mean (95% CI)</td>
<td>2.8 (1.5, 4.0)</td>
<td>4.7 (3.5, 5.9)</td>
<td>5 (3.3, 6.7)</td>
<td>4.1 (3.4, 4.9)</td>
</tr>
<tr>
<td>Work time missed due to DUs, % (95% CI)</td>
<td>3.0 (1.4, 4.6)</td>
<td>4.4 (3.0, 5.9)</td>
<td>5.4 (3.2, 7.6)</td>
<td>4.3 (3.5, 5.2)</td>
</tr>
<tr>
<td>Impairment due to DUs while working, % (95% CI)</td>
<td>26.5 (22.5, 30.5)</td>
<td>39.9 (36.2, 43.7)</td>
<td>45.4 (40.5, 50.3)</td>
<td>36.7 (34.2, 39.2)</td>
</tr>
</tbody>
</table>

*Includes 7 patients with missing information on number of DUs; †Number of employed/self-employed patients who gave information about working hours missed, normal working hours, and productivity impairment; ‡100×[Hours missed during month]/[4.3×Normal working hours per week]; §Converted from original scale: 0–10; CI: confidence interval; DU, digital ulcer.

Association between number of DUs and daily activity impairment
Responses to the daily activity question revealed that DUs had a considerable impact during the prior month. On average, the 2179 patients who completed the daily activity section of the questionnaire reported that DUs had impaired their ability to perform their regular daily activities by 50% (Fig. 2). Mean daily activity impairment worsened with number of DUs from 34.5% in patients with 0 DUs to 53.7% in those with 1–2 DUs and to 62.7% in those with ≥3 DUs.

Association between number of DUs and need for help
DUs were responsible for patients needing help from others. The 2226 patients who completed the help due to DU disease section of the questionnaire reported they required 6.6 (95% CI = 5.2, 7.9) mean hours of paid help and 36.7 (95% CI = 32.9, 40.5) mean hours of unpaid help in the prior month (Fig. 3). Mean hours of paid help needed increased with the number of DUs, from 2.0 hours in patients with 0 DUs to 8.7 hours in those with 1–2 DUs and to 8.8 hours in those with ≥3 DUs. Mean hours of unpaid help also increased with the number of DUs, from 17.0 hours in patients with 0 DUs to 35.9 hours in those with 1–2 DUs and to 63.7 hours in those with ≥3 DUs.

Discussion
The present results are based on assessments from the DUO Registry, the largest DU-specific registry currently available (15). These analyses comprised 2327 patients from 18 European countries. Previous studies that evaluated the impact of DUs in SSC patients in clinical practice included fewer patients, and each study was conducted in a single country (5-7, 10, 11, 16-19).
The present analyses extend prior investigations—none of which assessed functional correlates of DUs by categorising patients by number of DUs—by establishing that the number of DUs (0, 1–2, or ≥3) was related to impairment of SSc patients’ general ability to work and perform daily activities, and their requirement for daily support. Additionally, patient burden, as measured by rates of complications and use of SSc-related medications (including prostacyclin and analgesics), mostly increased with number of DUs.

Patients’ self-completed functional assessments in the DUO Registry pointed to a major impact of DUs on work, supporting findings from earlier studies (7, 10, 11). Among 113 patients with SSc who were in the workforce, Bérezné et al. found a mean self-reported productivity decrease of 1.4 on the 0–10 scale from the questionnaire (developed by Actelion for DU, which was provided to Bérezné et al. for use in their study) (7). This estimate cannot be compared directly with the DUO Registry findings because Bérezné et al. included a high proportion (40%) of SSc patients with no past or current DUs, which may have contributed to the apparently low work impairment in their study. In addition, the study by Bérezné et al. was conducted in a single country only, whereas the DUO Registry comprises many European countries. The impact of disease on work impairment is expected to vary depending on the social security system and other characteristics of the country in question.

In the DUO Registry, work hours missed, productivity impairment while working, and overall work impairment all increased with number of DUs. On average, overall work impairment was approximately 20% higher (in absolute percentage terms) among patients with ≥3 DUs than among those with none. Two prior studies investigated the relationship between different measures of DU severity and work disability: Sandqvist et al. described 48 patients of working age with SSc and found that self-rated DU symptoms (such as pain, fatigue, and impaired hand function) were significantly associated with ability to work (11). Toffolo et al. measured ulcer dimensions and administered the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire to 24 patients with SSc, revealing increasing work impairment with larger ulcer dimensions (10).

As in previous investigations (7, 19), the present analysis found no effect of DUs on the percentage of employed/self-employed patients. However, the presence of DU, alone or associated with other clinical manifestations, is directly associated with disability because of pain and limited possibilities to perform the most simple tasks in daily life, such as housekeeping, or any work involving the hands (11). Thus, DUs may have an impact on employment and influence the types of work done over the course of the disease.
but the study design and assessments in this and previous analyses may have been unable to address such differences. Present results demonstrate that DUs severely impair SSc patients’ ability to perform daily activities. The average impairment of 50% found in this analysis, across all three DU categories (34.5%, 53.7%, and 62.7% in patients with 0, 1–2, and ≥3 DUs, respectively), was similar to that reported for 60 patients with DUs assessed by Bérezné et al., who estimated a mean impairment of daily activities of 48% (7). Findings are also broadly consistent with recent data for patients with SSc from the Canadian Scleroderma Research Group Registry who reported at least sometimes experiencing DUs. Of these patients, 91% said that DUs had at least moderate impact on their daily activities (impact response options: no impact, minimal, moderate, severe and extremely severe) (9).

Moreover, mean daily activity impairment in the DUO Registry was 1.5 times higher among patients with 1–2 DUs and nearly twice as high in those with ≥3 DUs, compared with patients with no DUs. Toffolo et al. also reported that daily activity impairment (assessed using the DASH) correlated significantly with severity of DUs as measured by diameter and area of DUs (10).

Data from the DUO Registry indicate that the need for help from others due to DUs increases with number of DUs. Compared with patients with no DUs, those with ≥3 DUs reported requiring approximately 6.8 and 46.7 more hours of paid and unpaid help, respectively. Bérezné et al. also found that a high proportion of patients with DUs needed both paid and unpaid household help due to DUs, though their data were not stratified by number of DUs (7). The 59 patients with DUs assessed by Bérezné et al. needed a mean of 3.8 hours per month of paid help and 15.0 hours per month of unpaid help. This represents less paid and unpaid help than the average in the present study (6.6 hours of paid help and 36.7 hours of unpaid help). The findings by Bérezné et al. are more similar to the results for patients with no DUs in the DUO Registry (i.e. 2.0 hours of paid help and 17.0 hours of unpaid help). Nevertheless, both studies point to a substantial need for help by patients with DUs associated with SSc.

This study is subject to a number of limitations. Different types of bias may have impacted results. Recall bias may be present, since patients had to remember and quantify their functioning during the previous month. Selection bias also cannot be excluded, because patients who did not complete at least one part of the functional assessment questionnaire differed in certain clinical and demographic aspects from questionnaire completers. In addition, social security systems vary among the countries included in the DUO Registry, which may have influenced results (e.g. due to level of payment in case of absence from work, and payment of home help).

Observed differences between categories based on number of DUs at enrolment could be due to differences in risk factors, SSc treatment, or SSc severity, rather than number of DUs per se. For example, patients with more DUs may have had higher overall SSc severity, which could have confounded the apparent association of some functional impairment measures with number of DUs. Supporting this possibility, the results indicated that patients with a higher number of DUs present at enrolment were younger, and had earlier disease symptoms. In the DUO Registry, the functional assessment questionnaire asks patients to indicate their functional limitations due to their DUs, thus the study design limits our ability to assess the contribution of the underlying SSc to functional impairment. It should be noted that although the questionnaire asks patients to report the impact of their DU on work, daily activities, and need for help, they may not always be able to attribute these to their DU disease, as opposed to their underlying SSc or their comorbidities. For example, in a recent survey of 556 SSc patients in Canada, 317 (57%) patients self-reported one or more of the following symptoms resulting in moderate or greater impact: hand stiffness, difficulty in making a fist, holding objects, opening their hand, and/or using a faucet (20). The DUO Registry was not designed to address the important question of whether employment rates differ between the general population and patients with DU disease, or to assess the impact of DU disease on employability, the type of work performed, or the need to change work.
Nearly 70% of the patients enrolled in the DUO Registry answered the functional assessment questions, thus implying good representativeness of the results. However, the ability to generalise results from this study is limited by the fact that the DUO Registry aims for high coverage of bosentan-treated patients with DUs associated with SSc, so the registry may have a higher proportion of bosentan-treated patients than the overall population seen in clinical practice. However, baseline demographic, clinical, and antibody characteristics of patients enrolled in the DUO Registry are similar to those in previously reported cohorts (12).

In conclusion, the present results reveal the heavy burden that DU disease imposes on patients with SSc, with respect to its association with work, daily activities, and need for paid and unpaid help, and also in terms of complications and need for medications. Greater patient morbidity and medication use, higher impairment of work and daily activities, and increased help received from others were reported in patients with increasing number of DUs. These results demonstrate that number of DUs is a clinically relevant endpoint assessing severity of DU disease and burden on patients. The ability of the DU-specific measures employed in the DUO Registry to detect differences in patient-relevant outcomes supports previous calls for the development of clinician- and patient-reported instruments of high specificity to the clinical impact of DUs for future studies of DU associated with SSc (21). In addition, results highlight the importance of predictive tools, such as videocapillaroscopy (22), to identify SSc patients at high risk for developing DU, as well as effective treatments to reduce the number of DUs in order to improve functioning and to reduce the disease burden in patients with SSc.

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DUO Registry investigators

Austria

Czech Republic
Faculty Hospital Bulovka, Prague, I Zemanova; Faculty Hospital Hradec Králové, Hradec Králové, T Soukop; Faculty Hospital Olomouc, Jesenik, A Smrzova; Faculty Hospital Ústí svate Jan Brno, Brno, J Bohmova, J Prochazkova, P Nemec; General Hospital Brno, Brno, Z Fojtik; General Hospital Plzen, Plzen, D Suchy; Institute of Rheumatology Prague, Prague, R Becvar

Denmark
Arhus University Hospital, Arhus C, AB Olsen, KH Sondergaard

Finland
Helsinki University Central Hospital, Helsinki, R Luosujärvi; Tampere University Hospital, Tampere, K-L Vildqvist

France
Centre hospitalier d’Albi, Albi, Médecine Interne, S Madauale; Centre Hospitalier de Le Mans, Le Mans, Dermatologie, N Beneton, H Maillard; Centre Hospitalier de Lille, Hôpital Claude Huriez, Lille, Médecine Interne, H Charlanne, F Granel-Brocard, E Hachulla, PY Hatron, N Jourdain, M Lambert, D Launay, S Morell, G Woitaski; Centre Hospitalier de Perpignan, Hôpital Saint-Jean Roussillon, Perpignan, Médecine Interne, O Cattray; Centre hospitalier de Valence, Valence, Dermatologie, F Skowron, Médecine Interne, T Zenone; Centre Hospitalier Universitaire d’Amiens, Amiens, Dermatologie, A Dadban, C Lok; Centre Hospitalier Universitaire de Besançon, Hôpital Jean Minjoz, Besançon, Médecine Interne, D Ferrandiz, N Magy-Bertrand, MP Moison; Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, Dermatologie, A Taieb, S Balquiere, E Belin, C Droitcourt, S Julien, S Prey, Médecine Interne, C Boulon, J Constans; Centre Hospitalier Universitaire de Bordeaux, Hôpital du Haut-Lévêque, Pessac, Dermatologie, M S Doutre, E Kostrzewa; Centre Hospitalier Universitaire de Bordeaux, Hôpital Pellegrin, Bordeaux, Rhumatologie, C Richez; Centre Hospitalier Universitaire de Brest, Hôpital Morvan-Dermatologie, Brest, M Greco, L Misery, B Sassolas; Centre Hospitalier Universitaire de Dijon, Hôpital du Bocage, Dijon, Médecine Interne, E Collet, S Berthier, V Leguy-Seguin; Centre Hospitalier Universitaire de Grenoble, Hôpital Michallon, La Tronche, Médecine Vasculaire, B Imbert, P Carpenter, S Blaise; Centre Hospitalier Universitaire de Limoges, Hôpital Dupuytren, Limoges, Dermatologie, A Couraud, V Doeff-Hantz, A Spars, Médecine Interne, H Bezanahary, N Boussely, S Dumonteil, AL Fauchais, G Goudran, V Loustaud-Ratti, P Manea, E Vidal; Centre Hospitalier Universitaire de Lyon, Hôpital Edouard Herriot, Lyon, Médecine Interne, B Coppere, H Desmurs-Clavel, MH Girard-Madoux, A Hot, J Ninet; Centre Hospitalier Universitaire de Marseille, Hôpital Nord, Marseille, Médecine Interne, B Ganel; Centre Hospitalier Universitaire de Montpellier, Hôpital Lapeyronie, Montpellier, Rhumatologie, J D Cohen; Centre Hospitalier Universitaire de Montpellier, Hôpital Saint-Eloi, Montpellier, Médecine Interne, A Keynote, A Khun van Kien, A Le Quellec, S Riviere, P Rullier, Dermatologie, D Bessis; Centre Hospitalier Universitaire de Nancy, Hôpital Central, Nancy, Médecine Interne, C Farças; Centre Hospitalier Universitaire de Nancy, Hôpital de Brabois, Nancy, Médecine Vasculaire, Vandoeuvre-les-Nancy, V Bravetti, T Moline, D Wahl, S Zally; Centre Hospitalier Universitaire de Nancy, Hôpital Maringer, Nancy,
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Zaragoza, L. Sáez; Hospital Universitario Ramón y Cajal, Madrid, A. Zea, C. De la Puente; Hospital Universitario Reina Sofía, Córdoba, FG Martínez, MA Aguirre; Hospital Universitario Severo Ochoa, Leganés, P Collado, A Cruz, M Crespo; Hospital Universitario Virgen del Rocío, Sevilla, J. Sánchez-Román, MJ Castillo; Hospital Virgen de la Salud, Toledo, AM García, G Muñiz

Sweden
Falú Lasarett, Falun, PJ Hedlin; Helsingborgs Lasarett, Helsingborg, C Stahl Hallengren; Blekingesjukhuset, Karlskrona, Karlskrona, T Bracin; Karolinska universitetssjukhuset, Huddinge, Stockholm, A Nordin, K Albertsson, Y Rydhvald; Spenshult sjukhus, Oskarström, C Thorsson; Universitetssjukhuset i Linköping, Linköping, E Hermansson

Switzerland
Rheumaklinik und Institut für Physikalische Medizin Universitätsspital Zürich, Zürich, B Maurer, D Verner, O Distler, R Schmidt-Bossard

United Kingdom
Addenbrooke’s Hospital, Cambridge, F Hall, K Murphy; Aintree University Hospital, Liverpool, J Lamb, M Anderson, R Moots; Chapel Allerton Hospital Leeds, Leeds, M Buch, L Bissell; Glasgow Royal Infirmary, Glasgow, R Madhok, R Hampson; Guy’s and St Thomas’ Hospital, London, D D’Cruz, LM Choong; King’s College Hospital, London, P Gordon, J Dobson, R Salerno; Queens Hospital, Burton on Trent, M Nisar, C Williams, L Wilcox; Royal Free Hospital, London, C Denton, R Ochiel, T Ngoziana, L Parker, R Vincent; Royal National Hospital for Rheumatic Diseases, Bath, N McHugh, S Cole, S Brown, J James; Salford Royal University Teaching Hospital, Manchester, A Herrick, J Manning, T Moore; Solihull Hospital - Heart of England NHS Trust, Birmingham, A Faizal; Southport and Formby District General Hospital, Southport, H Skyes; The Ulster Hospital, Belfast, A Smythe, A Hamilton

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