

# Infections of scleroderma digital ulcers: A single center cohort retrospective study

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## Abstract

Systemic sclerosis (SSc) is a complex autoimmune and up to 50% of patients develop digital ulcers. We revised fifty consecutive patients with SSc-related digital ulcers (DUs) who referred to our Scleroderma Unit. Thirty-five of them who showed clear signs of DUs infection underwent to cutaneous swab and microbiological data collection. We performed 87 cutaneous swabs overall. DUs were recurrent in 58% of the patients and multiple in 60% of patients. Fourty-four swabs (53%) were positive for *Staphylococcus aureus* (13% Methicillin-Resistant), 9 (10%) were positive for *Pseudomonas aeruginosa*, and then the others less frequently isolated. Nine patients (25%) needed hospitalization. Our data support a patient-tailored approached to DUs, particularly those infected. Self-hygiene and asepsis during dressing procedures are mandatory. Patient must be trained to avoid dangerous behaviors and reduce the risk of infection.

## Introduction

Systemic sclerosis (SSc) is a complex autoimmune disease characterized by vascular damage, immune activation and fibrosis of skin and internal organs.<sup>1,2</sup> One of the most frequent and severe SSc manifestations are digital ulcers (DUs) related to systemic vasculopathy. DUs are present in up to 50% of patients affected by SSc,<sup>3</sup> they are often difficult to heal, recurrent and cause pain and disability. Sometimes DUs could become infected exposing patients to severe complications (osteomyelitis and gangrene) related to a worst prognosis of the disease.<sup>4,5</sup> The management of SSc-related DUs remain challenging: they affect patient's quality of life and frequently led to work disability with a significant impact on

healthcare costs.<sup>6</sup> There is a scarce number of scientific publications on infectious complications of SSc-related DUs and any study has addressed the impact of infection on the DUs' healing process.<sup>6-8</sup> In the present study we retrospectively revised microbiological findings from scleroderma digital ulcers and suspected bacterial infection.

## Materials and methods

We revised fifty consecutive patients with SSc-related DUs who referred to our Scleroderma Unit during the last twelve months. Thirty-five of them (33 females and 2 males; mean age 65±13 years, disease duration 14±6.7 years), showed clear signs of infection in at least one DUs. According to the European Wound Management Association (EWMA) position document,<sup>9</sup> infected DUs only were microbiologically tested by means of a cutaneous swab. We considered signs of possible infection: perilesional erythema, swelling, purulent exudates, distinctive odor and presence of pain.<sup>10</sup> All patients fulfilled EULAR/ACR classification criteria for SSc.<sup>11</sup> Patients were carefully evaluated based on clinical records, clinical and serological findings, DUs' characteristics and a complete *wound assessment*.<sup>3,12</sup> DUs were defined as loss of both surface epithelialization and dermis; other manifestations, such as fissures or post-traumatic skin lesions, were excluded.<sup>3</sup> We performed 87 cutaneous swabs overall at the level of the DUs' bed after removal of dried exudates, slough or dressing residue. We used sterile cotton swab, with ringer lactate-moistened tip in case of extreme wound dryness. Swab was woven side-to-side and rotated at the same time, following the Levine technique.<sup>5,13,14</sup> We collected materials either from the wound bed and the wound margins. Microorganism detection was performed by means of agglutination tests with antibodies for bacterial surface specific antigens, using protein or DNA sequencing.

## Results

Data of the fifty SSc patients with DUs were reported in Table 1.

Thirty-five patients had infected DUs. Most of our patients were on systemic i.v. prostanoid therapy (42 pts) alone or in combination with endothelin receptor antagonist (bosentan, 25 pts), dual endothelin receptor antagonist (macitentan, 7 pts), phosphodiesterase 5 inhibitor (sildenafil, 3 pts) and oral nifedipine (12 pts). All DUs were local-

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ized on the acral zone of the hands (fingertips 90% of times) while only one DU was localized to toe tips. DUs were recurrent in twenty patients and in twenty-one patients we detected multiple skin lesions at a time. Regarding the thirty-five patients with infected DUs (2 M/33 F, mean age 65±13 years, mean disease duration 14±11 years),

twenty-four of them experienced recurrent DUs and twenty-one had multiple DUs. Most of our patients had a limited SSc subtype (25pts) and anticentromere autoantibodies were the most frequently extracted (20 pts). Among the eighty-seven swabs, only four of them were negative, while eighty-three were positive for the presence of microorganisms. Forty-four (53%) swabs were positive for *Staphylococcus aureus* (*S. aureus*); 9 (10%) were positive for *Pseudomonas aeruginosa* (*P. aeruginosa*), 7 (8%) for *Escherichia coli* (*E. coli*), 6 (7%) for *Enterococcus faecalis* (*E. faecalis*), 5 (6%) for *Streptococcus epidermidis* (*S. epidermidis*) and 3 (3%) for *Bacillus morganii*. Interestingly, 6/44 (13.6%) positive swabs for *S. aureus* infections showed a methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, nine patients with infected DUs needed hospitalization. All infections responded to systemic antibiotics therapy except for MRSA which required a more aggressive and long lasting (up to fourteen consecutive days) antibiotic combination therapy in addition to surgical

debridement and hygiene procedures. There is a lack of robust in vivo data for using topical antimicrobials/antiseptic for managing infected wounds. Topical antiseptic therapy could be related with toxic effects on human cells and some laboratory tests have limited their clinical use.<sup>15</sup> Even local antimicrobial agents could induce adverse effects and they are related to allergy and bacteria resistance.<sup>9</sup> In scleroderma patients with more severe skin involvement the use of antiseptic and antimicrobial local therapy are also related, in our experience, with excoriation in the peri wound skin, discomfort and pain.

Fecal pathogens, rapidly improved with standard therapy but were more frequently responsible for reinfections. Furthermore, our analysis showed a prevalence of *S. aureus* (82%) or *S. epidermidis* (8%) infection in patients with a limited SSc subtype, while MRSA infection increased significantly in patients with previous and recurring DUs infections (6/6) and/or with past history of hospitalization (6/6). Disease duration, serology, age, gender or smoking habits did not correlate with the presence of

DUs infections.

Twenty-three patients got re-infected in the same DUs in an extremely variable period of time, depending on, for example: disease progression rate, immunodeficiency status, modified Rodnan skin score, disease subtype (lcSSc vs dcSSc), presence/absence of finger contraction, Raynaud phenomenon severity.

We assessed the improvement of the infection monitoring for infection clinical signs such as pain, the presence of exudate and smell. We also checking DUs dimensions such as length, width, or depth, and chromatic parameters, such as the colors of granulation or necrotic tissue in the wound bed, pallor, or erythema of surrounding skin.

## Discussion

Our study reported the prevalence of DUs infections in SSc patients during a twelve-months follow-up. Among the eighty-seven swabs performed on DUs with clinical signs of infections the overall confirmation of infection was in eighty-three of them (95.4%), with four only negative samples. Clinical assessment of DUs and particularly the evaluation of signs and symptoms of DUs infection, acquires a pivotal role highlighting that diagnosis of DUs infection is primarily a clinical skill<sup>3</sup>. Our report firstly showed pathogens' resistance in DUs infections, in particular MRSA. SSc-related DUs are *per se* difficult to heal and infections complications, as gangrene and osteomyelitis, are related with a worse prognosis of the disease.<sup>4,5,16</sup> Wound infection is one of the most challenging aspects of wound management and a major contributor to healthcare costs worldwide. Nonetheless we are missing robust data about infectious complications of SSc-related DUs and about the impact of infection on DUs' healing.<sup>17,18</sup> Exogenous microorganism could be spread by the environment, by health care personnel during dressing, by contaminated medical equipment or even by the patient him/herself. In 2012,<sup>5</sup> we reported that fecal pathogens were found to be present in 26% of SSc-related DUs infections but in the present paper we reported a prevalence of just the 15% (*E. coli* + *E. faecalis*). Those new data are particularly intriguing because from 2012 we have been training our patients with prominent attention to hand hygiene. We strongly recommend the use of individual protection devices as disposable gloves or sterile dressing for self-medication. Those precautions have probably caused a reduction in some pathogens favoring ubiquitous ones

**Table 1. Clinical and serological data overview.**

Clinical and serological data	Total	Infected digital ulcers
Systemic sclerosis patients, N	50	35
Male/female	3/47	2/33
Age, mean SD years	64±13	65±13
Disease duration, mean SD years	13±10	14 ±11
Smokers/non-smokers	13/37	10/25
Skin subsets, N		
Limited cutaneous	35	25
Diffuse cutaneous	15	10
Serology, N		
Anti-Scl-70	12	7
Anticentromere	28	20
Other antinuclear antibodies	10	8
Therapy, N		
Systemic i.v. prostanoid	42	28
Bosentan	25	16
Macicentan	7	6
Oral nifedipine	12	6
Sildenafil	3	1
Digital ulcers (%)		
Recurrent DUs	58	68
Multiple DUs	60	60
Fingertip ulcers	90	85.7
Hospitalization	20	25.7
Swabs, N. (%)		
Positive swabs		83 (95)
<i>Staphylococcus aureus</i>		44 (53)
<i>Pseudomonas aeruginosa</i>		9 (10)
<i>Escherichia coli</i>		7 (8)
<i>Enterococcus faecalis</i>		6 (7)
<i>S. epidermidis</i>		5 (6)
<i>M. morganii</i>		3 (3)
Others*		9 (10)

\**C. albicans*, *K. pneumoniae*, *Citrobacter freundii*, *S. agalactiae*, *Acinetobacter ursingii*, *Stenotrophomonas maltophilia*, *Acinetobacter gyllenbergi*, *Serratia marcescens*, *Trichophyton interdigitale*.

like *S. aureus*. These Gram-positive bacteria is the most frequently isolated pathogen (followed by *P. aeruginosa* and *S. epidermidis*) particularly in patients on immunosuppressive therapy (mycophenolate mofetil, anti-CD 20 antibodies, azathioprine). In our database, MRSA constitute the 6% of every infection, are responsible for the 100% of our pathogen-resistant infection and are related with multiple/recurrent DUs and subsequent history of hospitalizations. Anyway, further studies are needed to better understand the role of resistant bacteria in DUs infections.

We are still lacking validated DUs' management guidelines with particular regard to those who became infected. We believe that the therapeutic approach of SSc-related DUs should be invariably patient-tailored on the basis of both general clinical conditions and careful evaluation of single skin wound. In particular, a correct therapeutical strategy should always be preceded by the assessment of each DUs, the presence of possible subclinical local complications (infections, osteomyelitis, gangrene), and/or comorbidities (district macrovascular involvement, diabetes, and other systemic disorders).<sup>19</sup> Systemic and local treatments encompass both pathogenetic and symptomatic drugs, as well as different non-pharmacological measures. Noteworthy, chronic and procedural pain treatments using systemic and local analgesics are definitely required.<sup>8,20,21</sup> Elevated standard of health care, self-hygiene and asepsis during procedures are mandatory as well as careful surveillance of the hospital environment. Patient must be trained to pay specific attention to avoid infections, because one of the most important reservoirs is the patients' endogenous flora (pathogens from the skin, mucous membranes and gastrointestinal tract). Our data support the need of a training of patients about the use of personal protections devices and there is clearly a need for further multicentric studies to better comprehend the role of infections in scleroderma DUs.

## Conclusions

Our data support a patient-tailored

approach to DUs, particularly those infected. Self-hygiene and asepsis during dressing procedures are mandatory. Patient must be trained to avoid dangerous behaviors to reduce the risk of infection due to their endogenous flora, which is, based on our data, patients' greatest reservoir.

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